Laws in Darwinian Evolutionary Theory

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Abstract

In the present article the recent works to formulate laws in Darwinian evolutionary dynamics are discussed. Although there is a strong consensus that general laws in biology may exist, opinions opposing such suggestion are abundant. Based on recent progress in both mathematics and biology, another attempt to address this issue is made in the present article. Specifically, three laws which form a mathematical framework for the evolutionary dynamics in biology are postulated. The second law is most quantitative and is explicitly expressed in the unique form of a stochastic differential equation. Salient features of Darwinian evolutionary dynamics are captured by this law: the probabilistic nature of evolution, ascendancy, and the adaptive landscape. Four dynamical elements are introduced in this formulation: the ascendant matrix, the transverse matrix, the Wright evolutionary potential, and the stochastic drive. The first law may be regarded as a special case of the second law. It gives the reference point to discuss the evolutionary dynamics. The third law describes the relationship between the focused level of description to its lower and higher ones, and defines the dichotomy of deterministic and stochastic drives. It is an acknowledgement of the hierarchical structure in biology. A new interpretation of Fisher's fundamental theorem of natural selection is provided in terms of the F-Theorem. The proposed laws are based on continuous representation in both time and population. Their generic nature is demonstrated through their equivalence to classical formulations. The present three laws appear to provide a coherent framework for the further development of the subject.

Contents

Nothing in Biology Makes Sense Except in the Light of Evolution

Theodosius Dobzhansky (1900-1975)

I. INTRODUCTION

A. Background

Darwinian evolutionary theory occupies a unique position in biological sciences. Progress in experimental biology and new data from field observation after the neo-Darwinian synthesis pose new questions to be answered and call attention to previously unanswered questions. One of the central questions is whether or not there exist general laws in biology. Biologists have been responding to those demands with tremendous activities (12; 18; 23; 24; 28; 32; 54; 65; 74). There was a critical discussion (34) of existing theories. Courageous exploration (40) of new theories was carried out to probe the origin of order. Serious consideration of the epistasis of gene interactions (82) was made. Shifting balance process (13; 31; 61) was reevaluated. There is a continuous interest in the concept of species (54; 63). The fundamental theorem of natural selection (15; 23; 33) has been constantly reexamined. Various elegant mathematical models of speciation (18; 28; 42; 72) were explored. Even new philosophical implications have been speculated (76) and discussed (54). Such efforts have enriched both quantitative and conceptual understanding of evolution.

It has been noted (82) that a quantitative formulation of evolutionary dynamics may be of most importance to answer the new questions. Verbal description has been found to be

inadequate, because the various deterministic and stochastic contributions to evolutionary dynamics, either independent or interactive, are often of same order of magnitude. Also, interactions can be highly nonlinear and cooperative behaviors are abundant. For example, it was from this consideration that Stewart (72) built his model based on symmetry-breaking and Gavrilets (28) advanced his holey adaptive landscape model. The present review develops further this line of research. We make an attempt to formulate a general and quantitative mathematical framework which appears broad enough to incorporate the ideas of nonlinear symmetry-breaking (72) and diffusion in the holey adaptive landscape (28). It is conceptually consistent with Darwinian dynamics. The formulation appears to capture the dynamical part of the evolution by natural selection (16; 17). In particular, two of the most influential quantitative concepts in evolutionary biology, the adaptive landscape of Wright (83) and the fundamental theorem of natural selection of Fisher (25), are built naturally into the present formulation, after their reformulations in the light of modern progress. The present work may also be regarded as an attempt to unify approaches on nonequilibrium processes from both biological and physical sciences.

B. Language of Mathematical Description

The mathematical approach in the present work is based on the continuous representation which treats both time and state variable (for example, populations of species in ecological dynamics and frequencies of genotypes in population genetics) as continuous variables. There are three reasons for choosing the continuous representation. First, since the continuous representation has been widely used in physical sciences, it would be easy to make connections to those fields. Second, from a mathematical point of view, any discrete process may be represented by an appropriate continuous one. Hence there is no loss in rigor to use continuous representation. Thirdly and most importantly, the connection between discrete and continuous representations has been well studied in biology, documented, for example, in both a commentated collection of historical articles (47), in a recent monograph (12) and in recent textbooks (23; 65), and in an online book (24), and has been successfully and widely employed in population genetics. Those studies provide the needed link between biological parameters appearing in real biological cases and the corresponding continuous representation. Such connection has also been studied in physical sciences (49; 77). Hence, in the

rest of present review we will not elaborate further on the appropriateness of continuous representation. This implies that the equations to be discussed are differential equations. To be more precise, we will postulate three laws for evolution and the most important law, the second law, will be expressed in the unique form of stochastic differential equation. The connection of the present three laws to well known classical formulations will be discussed. The logical consistency of the postulated laws will be emphasized, which results in a flavor of abstractness in the present presentation.

C. What to Be Discussed

Apart from a concise review of literature, it should be stated here that the focus of the present article is the structure of evolutionary dynamics, that is, how many independent dynamical components should be there, what should be their nature, and which form the governing dynamical equation should be taken. We will not discuss the structure of each dynamical component. Making an analogy to classical physics, what we shall attempt to review and to establish below is similar to Newton's laws of motion, not of the structure of mass and force, such as his law of gravity. Hence, the content of present article corresponds largely to that when Darwin and Wallace published their theory of evolution by natural selection (17): there are laws of evolutionary dynamics, but the underlying structures for dynamical components, such as those related genetics, will not be discussed but are assumed to exist. This implies that many quantitative and important problems, such as the speed of evolution (62), cannot be discussed in the present review, because the knowledge of the dynamical component structure is needed for such discussions.

D. Organization of Topics

We organize the rest of the present review style article as follows. In section II recent efforts in both biological and physical sciences on the quantitative formulation of evolutionary dynamics are reviewed. In section III we postulate and discuss the three laws of evolution. Four dynamical elements will be introduced and discussed. Fisher's fundamental theorem of natural selection is reinterpreted as the F-Theorem. In section IV the connection of the postulated three laws to classical formulations is discussed. An example of such a connec-

tion will be explicitly demonstrated in section V. The F-Theorem is further discussed in section VI. Implications of present formulation are discussed in section VII. Further notes on selected references are presented in section VIII. Section IX summarizes the results of the present article.

II. EFFORTS ON QUANTITATIVE FORMULATION OF EVOLUTIONARY DYNAMICS

In this section we review the previous efforts on the formulation of evolutionary dynamics. No complete, and even no comprehensive, coverage of literature is claimed. Nevertheless, we do wish to convey the message that there have been considerable progress and that controversies still exist.

A. Ronald Alymer Fisher and Sewall Wright

Fisher and Wright are among most prominent figures who laid down the mathematical foundation for the modern quantitative analysis in population genetics (67). Their seminar works were among those that marked the start of neo-Darwinian synthesis. In 1930, Fisher proposed the fundamental theorem of natural selection (25), likening it to the second law of thermodynamics in physics. In 1932, Wright proposed the evolutionary adaptive landscape in attempting to quantify and to visualize the fitness in evolutionary dynamics (83). The mathematical developments in population genetics since then have been recently summarized, for example, by Ewens (23) in an effort to discuss and to contrast the views of Fisher and Wright and to find a common basis for further development of the field. However, a considerable amount of controversies still exist around those central concepts of Fisher and Wright.

It is a consensus that there is no final formulation of Fisher's fundamental theorem of natural selection. Ewens himself has changed his interpretation of this theorem between the first and second editions of his book and considers that the fundamental theorem of natural selection is still in the developmental stage. According to Ewens, the original formulation by Fisher was very obscure, but Ewens holds the view that the theorem is indeed fundamental. He analyzed various concrete cases to illustrate the broad implications of this theorem (23).

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It may be concluded that in all those examples there is a common thread: the equivalence between the increase in fitness and the variation in evolution. Same subject has been also extensively discussed by Michod (55) and similar conclusion has been reached.

The adaptive landscape concept of Wright is in a slightly better situation. Its essence has been elegantly summarized by Ewens (23), if interpreting the "the surface of mean fitness" as the adaptive landscape:

"Wright proposed a three-phase process under which evolution could most easily occur. This view assumes that large populations are normally split up into semi-isolated subpopulations, or demes, each of which is comparatively small in size. Within each deme there exists a genotypic fitness surface, depending on the genetic constitution at many loci, and in conformity with the 'increase in mean fitness' concept, gene frequencies tend to move so that local peaks in this surface are approached. The surface of mean fitness is assumed to be very complex with multiplicity of local maxima, some higher than others. If a full deterministic behavior obtains the system simply moves to the nearest selective peak and remains there. The importance of the comparatively small deme size is that such strict deterministic behavior does not occur: random drift can move gene frequencies across a saddle and possibly under the control of a higher selective peak. Random changes in selective values can also perform the same function."

Here the important concept of the adaptive landscape implied in the "surface of mean fitness" has already been widely used in population genetics and is particularly illustrative in the discussion of speciation (18; 28; 42; 72). Such metaphoric and visualizing part of Wright's concept has prevailed in population genetics in particular and biology in large, and has even permeated into other fields such as statistical physics (70) and cosmology (71). Connections between those fields and Darwinian dynamics were already recognized by Lord Kelvin and by Boltzmann, two of the greatest physicists in 19th century, during the time of Darwin. It is interesting to note that ideas inspired by Darwinian dynamics have also been used in modern quantum physics (87). Nevertheless, the quantitative part of Wright's concept has remained an open question in biology. For example, the statement that no simple explicit formula is known for the stationary distribution (23) may be viewed as such a doubt.

A more explicit negative statement can be found in a recent textbook by Rice on mathematical foundation of population genetics. It is based on a perceived absence of potential in

limit cycle dynamics: "In fact, there is no general potential function underlying evolution. All that we need to do in order to demonstrate this is find a case in which, under selection alone, the allele frequencies in a population do not settle down to a stable point, but rather continue changing forever. We have already see an example of this in Figure 1.2. The fact that selection can result in limit cycles (see Figure 1.2B), in which the population repeatedly revisits the same states of some function that increases every generation. Note that this is not a contradiction of the fundamental theorem, since the frequency-dependence that drives the fluctuations is part of the $E(\delta w)$ term in Equation 1.52. Though evolutionary theory is not built on the idea that any quantity is necessarily maximized, the idea that there is such a quantity remains one of the most widely held popular misconceptions about evolution" (65). We will come back to Rice's statement in section V.

We believe that one of key ingredients to properly understand the works of Wright and Fisher is to re-interpret and to express them precisely in the light of the modern context of physics and mathematics, and to show that they are already implicitly contained in the classical formulations. This will be carried out in section III and IV.

B. Ecological Evolution

The evolutionary dynamics from the ecological point of view has been explored in rather detail. The efforts have been summarized, for example, in a recent monograph by Turchin (74). This author takes the view that general laws should exist and should give rise to useful results relevant to ecology. In particular, such a general framework should serve a constructive role from the following three aspects when confronting biological data: defining what one wants to explain; translating verbal theories into explicit mathematical models; and using formal statistical methods to quantify relative ability of rival models to predict data. Such a view is apparently valid in a broader context in biology demonstrated in the present article.

In order to provide a consistent mathematical starting point for ecological dynamics, Turchin has proposed six postulates, inferred four principles, and stated three dynamical classes. For example, his six postulates read: (1) The number of organisms in a population can change only as a result of births, deaths, immigrations, and emigrations; (2) Population mechanisms are individual-based; (3) There exists an upper density bound; (4) At

low resource densities the number of resource individuals encountered and captured by a single consumer is proportional to resource density—-mass action; (5) The amount of energy that an individual consumer can derive from captured resource, to be used for growth, maintenance, and reproduction, is a function of the amount of captured biomass—-biomass conversion; (6) No matter how high the resource density is, an individual consumer can ingest resource biomass no faster than some upper limit imposed by its physiology—-maximum consumption rate. The principles of population dynamics inferred by Turchin provides a basis to classifying dynamics as qualitative kinds of dynamical behaviors, the dynamical role of various mechanisms, and null hypotheses for testing consequences of dynamics. Those postulates and principles do appear to provide a consistent base for analyzing the ecological data. We refer readers to Turchin's book for a detailed exposition.

While we share Turchin's positive view on mathematical laws in biology, particularly about their existence and importance, there do exist several important differences on how such a general formulation should be carried out. On the conceptual level, it appears that Turchin has not differentiated between the laws of structure of evolutionary dynamics and the laws of the structures of constituents in the dynamical equations. This may not be crucial, because it is possible that in ultimate laws the structure of dynamics and the structure of the dynamical components may couple to each other, such as in Einstein's theory of general relativity where the mass and gravity are coupled to space and time. Nevertheless, we believe that there is a long way to reach such a state in biology and that it would be better to start with the situation that those two aspects of laws are decoupled. Another important difference is that the crucial role played by stochasticity has not been emphasized in Turchin's formulation. As a result, the evolutionary potential and Fisher's fundamental theorem of natural selection are not among Turchin's explicit topics.

On the technical level, it appears that the number of postulates in Turchin's formulation is too large and the postulates are too detailed even for the ecological dynamics. However, none of these differences consists of an objection to the truth in Turchin's formulation. They are rather the matter of choosing starting point from the mathematical point of view, that is, which set of axioms would be more convenient. The present formulation of population genetics will start from a different set of axioms. We believe that the same set of axioms also applies to the formulation of ecological dynamics. We will come back to Turchin's formulation on his first and most important principle after the exposition of our formulation

of evolutionary dynamics in section VIII.

C. Ilya Prigogine

The evolutionary dynamics may be classified into the realm of nonequilibrium processes. In this regard, no contemporary scholar has done more than what Prigogine had done. He had long recognized that nonequilibrium may be a source of order. He had also extensively investigated and forcefully generalized the physics' equivalence of Fisher's fundamental theorem of natural selection, the fluctuation-dissipation theorem, first systematically formulated by Onsager in 1931 (60). The importance of fluctuation has been summarized in his statement that both the dissipative structure and order are generated through fluctuations. His work had been condensed into his visionary theory of dissipative structure. A best place to gain insights into his theory and the work of his school may be the monograph written by Nicolis and Prigogine (59).

The compatibility of physical and biological sciences had been emphasized by Prigogine, if somewhat biased towards the former. It is stated (59) that "far from being outside nature, biological processes follow from the laws of physics, appropriate to specific nonlinear interactions and to conditions far from equilibrium" and that "thanks to these specific features, the flow of energy and matter may be used to build and maintain functional and structural order". Those understandings have now formed the basis in the study of biological processes. However, even with such a strong conviction, one of most important concepts in physics, the potential, has been concluded not applicable in general (59). We will come back to this point in section V. It should be mentioned that the approach of the Prigogine school is the best example of the classical approaches discussed below.

D. Potential in Nonequilibrium Dynamics

The usefulness of a potential function in a nonequilibrium process has long been fully recognized in physical sciences. As will be discussed in the present article, such a quantity can give both quantitative and qualitative description of behaviors near steady state or metastable states, such as the distribution function, the life time of metastabe state, etc. Despite the negative opinion on its existence reached by many researchers (14; 59), great

efforts have been spent to find such a potential function and to implement it in applications ever since the work of Onsager in 1931 (60).

Till 1990's, results of such efforts have been summarized, for example, in two excellent books by van Kampen (77) and by Risken (66), respectively. Nevertheless, in general such an effort has been regarded as not very successful (14; 59). The situation may be stated as follows. First, there was no general useful method for the construction of a potential function. Second, if viewing the log of the steady state distribution function as potential, it is not clear how this potential can be related to the dynamic trajectory of the system. Phrasing in a different way, it is known that the extremal points of so defined potential function do not necessary coincide with the fixed points of the drift force. How and why such a mismatch occurs has not been well understood yet.

The concept of potential in both dynamical and statistical contexts has been so useful that many researchers simply believe in its existence. There have been continuous efforts on the construction of potential function and related topics despite the doubt (14). Nice results have been obtained in several directions. Tanase-Nicola and Kurchan (73) has explicitly considered the saddle points of gradient systems by extending a super-symmetry method. They started from the existence of potential function to avoid the most difficult problem of the irreversibility: breaking of the time-reversible symmetry. The result is a powerful computational method to count the saddle points and to compute the escape rate.

The study of the mismatch of the fixed point of the drift force and those of extremals of steady state distribution has been reviewed by Lindner *et al.* (48) in the context of excitable systems widely encountered in physics, engineering, and biology. Rich phenomena have been observed by computer simulations. The mismatch has been treated as an numerical experimental discovery: At this moment there is no mathematical or theoretical explanation on why and how it should happen.

In another survey the useful and constructive role played by the noise has been summarized (81). It is argued there that the noise should play an important role in bringing out useful functions and order, much in the same reasoning as that of Nicolis and Prigogine (59) but emphasizing on the recent progress. Again, the above mismatch problem is encountered and the constructed potential function is typically regarded as approximation.

From an apparently different direction, there has been an effort to provide a solid foundation for non-equilibrium processes based on so-called chaotic hypothesis. Under the chaotic

hypothesis an interesting and important fluctuation theorem has been obtained, which further suggests the existence of the Boltzmann-Gibbs type steady state distribution function. Hence, a potential function is very likely to exist under this situation. The difficulty with this approach is that extremely few real physical systems have been shown to satisfy the chaotic hypothesis. It is not clear how the mathematical construction connects to the physical world. Such effort has been reviewed by Evans and Searles (22).

Because the metastability is such an important phenomenon and because of the difficulty encountered in the construction of potential function, effort has been made to go around the potential function problem but still to be able to compute the life time of metastable states. Such endeavor results in the so-called Machlup-Onsager functional method, summarized by Freidlin and Wentzell (26). It has been actively pursued (11; 50). It is an open question that how does this approach connect to those based on potential function, such as represented by Kramers' escaping rate formulae (43).

It is clear that the research on the construction of potential in nonequilibrium processes mirrors the effort on the adaptive landscape in biology.

III. LAWS OF EVOLUTIONARY DYNAMICS

In this section we postulate and discuss three laws in evolutionary dynamics. A few of their immediate and important empirical consequences will be discussed. They form a quantitative and consistent mathematical framework for evolutionary dynamics. We also discuss Fisher's fundamental theorem of natural selection and reformulate it as the F-Theorem. In particular, we will show that it is indeed an indispensable relationship in the present formulation.

The rationales to choose the postulation form of presentation are as follows.

On the positive side, there exist ample empirical evidences that the domain of population genetics is self-contained. Postulating the laws would be a direct manner to acknowledge this autonomous nature of population genetics. This also allows us to introduce the Wright's adaptive landscape and Fisher's fundamental theorem of natural selection at the very beginning. Then we can show that the present formulation is equivalent to the classical formulations. The ultimate importance and correctness of the present formulation lies in its ability to connect to empirical facts. We will point out such connections along with our

presentation.

On the other hand, there exist no rigorous derivations that the basic mathematical equations in population genetics can be obtained from more fundamental and microscopic laws in physics and chemistry. These equations in population genetics, which will be named classical formulations in the present review, do appeal reasonable, natural and well supported by empirical facts. We take the note that there exists no evidence either that they are incompatible with laws in physics and chemistry. Because we will not attempt the derivations of the present three laws, we have to choose a suitable starting point. In addition, it has been difficult to make the Wright's adaptive landscape and Fisher's fundamental theorem of natural selection explicit from the classical formulations, because they have been controversial since they were proposed seventy years ago as discussed in subsection II.A and II.D.

The numbering of postulated laws is arbitrary, with an arbitrary criterion to place the important one in the middle. We start with the most important and quantitative law, the second law.

A. Second Law: the Law of Darwin

The central questions are how to describe the evolutionary dynamics quantitatively and what are the dynamical elements. To be specific, let us consider an n component biological system. The n components may be the species in an evolutionary game (52; 74), the traits to describe the speciation (55; 72), genes in the description (23; 42), or any quantities required to specify the system. The additional example is that $\mathbf{q}$ can be the independent genotypic frequencies in population genetics (23). The value of jth component is denoted by q_j. The n dimensional vector $\mathbf{q}^\tau = (q_1, q_2, ..., q_n)$ is the state variable of the system. Here the superscript τ denotes the transpose. The dynamics of the state variable is described by its speed $\dot{\mathbf{q}} \equiv d\mathbf{q}/dt$ moving in the state space.

It is known that the Darwinian evolutionary dynamics is highly complex (16; 17; 32; 54; 57): the variation exists; there is a selection; and the dynamics is adaptive. To adequately capture its characteristic, we postulate that the dynamics of the system in evolution is governed by a stochastic differential equation, which consists of four dynamical elements. These are the positive semi-definite symmetric ascendant matrix A, the anti-symmetric transverse matrix T, the scalar function named the Wright evolutionary potential ψ, and

the stochastic drive ξ. The equation reads:

$$[A(\mathbf{q}) + T(\mathbf{q})]\dot{\mathbf{q}} = \nabla\psi(\mathbf{q}) + \xi(\mathbf{q}, t) \ . \tag{1}$$

This equation is supplemented by the following relationship between the stochastic drive and the ascendant matrix:

$$\langle \xi(\mathbf{q}, t)\xi^{\tau}(\mathbf{q}, t')\rangle = 2A(\mathbf{q}) \ \epsilon \ \delta(t - t') \ , \tag{2}$$

and $\langle \xi(\mathbf{q}, t)\rangle = 0$. The average $\langle ...\rangle$ is carried over the dynamics of the stochastic drive, not over $\mathbf{q}$, and ∇ is the gradient operator in the state space. To ensure the independence of the dynamics of each component, we assume

$$\det[A(\mathbf{q}) + T(\mathbf{q})] \neq 0 \ . \tag{3}$$

Here $\delta(t)$ is the Dirac delta function. In Eq.(2) we have assumed that the stochastic drive is a Gaussian white noise with zero mean. Factor 2 is a conventional choice for the present formulation, and ϵ is a positive numerical constant, which for many situations can be set to be unity, $\epsilon = 1$, without affecting the biological description. The relationship between the stochastic drive and the ascendant matrix expressed by Eq.(2) guarantees that the ascendant $A(\mathbf{q})$ is positive semi-definite and symmetric.

We leave the more detailed discussion on its connection to empirical data in section IV when discussing its equivalence to the classical formulations. In the remainder of this subsection a few the immediate and important consequences will be discussed.

It is straightforward to verify that the symmetric matrix term is 'ascendant':

$$\dot{\mathbf{q}}^{\tau} A(\mathbf{q})\dot{\mathbf{q}} \geq 0 \ . \tag{4}$$

Its dynamical effect is to increase the Wright evolutionary potential $\psi(\mathbf{q})$. Here we point out that the graphic representation of the Wright evolutionary potential corresponds to the adaptive landscape originally conceived by Wright. Here and below we avoid the loaded term *fitness* whenever possible. The Wright evolutionary potential defined here has clear meanings in both dynamics and equilibrium, while the fitness sometimes does not. The metaphor of adaptive landscape is extended to include all contributions which may affect the evolution in the considered process. The ascendant matrix enables the systems to have the tendency to seek the largest potential maximum (highest potential peak). This feature

will be explicitly manifested in the discussion after the first law. The anti-symmetric matrix leads to no change in potential:

$$\dot{\mathbf{q}}^\tau T(\mathbf{q})\dot{\mathbf{q}} = 0 \;, \tag{5}$$

therefore it is conservative. Dynamically it tends to keep the system along the equal evolutionary potential contour. A manifestation of the transverse dynamics is the oscillatory behavior. The effect of the stochastic drive $\xi(\mathbf{q}, t)$ on the motion in the adaptive landscape is random: It may either increase or decrease the evolutionary potential, that is, it may move up or down in the adaptive landscape. With the above interpretation, the steady state effect of natural selection is represented by the gradient of evolutionary potential, $\nabla \psi(\mathbf{q})$. The clear and graphical discussion of the Wright evolutionary potential was first explicitly expressed by Wright (83) in his concept of adaptive landscape: the potential peaks corresponding to the Wright's fitness peaks. The evolutionary potential introduced here is a generalization of Wright's original concept. The tempo of natural selection is represented by the ascendant and transverse matrices. Eq.(1) states that the four dynamical elements, the gradient of Wright evolutionary potential, the stochastic drive, the ascendant dynamics, and the transverse dynamics, must be balanced to generate the evolutionary dynamics.

Eq.(1) is the fundamental equation of evolutionary dynamics expressed in the unique form of stochastic differential equation: a form to our knowledge has neither been used in population genetic nor been generally discussed in mathematically literature. In accordance with above discussion on stochastic drive and ascendant matrix, we may call the supplementary equation, Eq.(2), the stochasticity-ascendancy relation. We will discuss it in the last subsection in this section in connection with Fisher's fundamental theorem of natural selection, and suggest to name Eq.(2) the F-Theorem.

The Wright evolutionary potential ψ introduced in the present review is in general a highly nonlinear function of state variables (the populations in ecology and gene frequency in population genetics). Its role is similar to that of energy in physical sciences in several aspects. It is in fact opposite in sign to the typical potential energy used in physical sciences. It is independent of time here. More precisely, the time variation of the Wright evolutionary potential is slow comparing to the time scales of the problem. Extension of present discussion to explicitly time depending case can be made. If the Wright evolutionary potential is bounded above, the stationary probability density to find the system at $\mathbf{q}$ in state space,

exists, and is expected to be a Boltzmann-Gibbs distribution:

$$\rho(\mathbf{q}, t = \infty) = \frac{1}{Z} \exp \left\{ \frac{\psi(\mathbf{q})}{\epsilon} \right\} . \qquad (6)$$

Here $Z = \int \prod_{i=1}^{n} dq_i \exp \{\psi(\mathbf{q})/\epsilon\}$, the partition function in physics, which is the summation over whole state space and serves as the normalization factor. Eq.(6) will be derived in next section as Eq.(38). Or it can be directly verified by inserting it into Eq.(39). For a reader who is familiar with Langevin equation in physics (30; 77), with $-\psi$ as energy and ϵ as temperature Eq.(6) may appear intuitively obvious. For a reader who is not familiar with the corresponding physics, a temporary trust on Eq.(6) till Eq.(38) and (39) or (42) is needed.

We should point out that the dynamical aspects of evolution, the transverse matrix T and the ascendant matrix A, do not explicitly enter into Eq.(6). This is similar to that of the energy function in classical physics. This suggests that the Wright evolutionary potential represents the final and ultimate selection of the evolutionary process. It describes the eventual landscape to which the system should be adapted. Nevertheless, the ascendant and transverse matrices, as well as the stochastic drive, do affect the time to approach to this steady state. From Eq.(6) we read that the larger the constant ϵ is, the wider the equilibrium distribution would be, and more variation would be, or, the smaller the ϵ is, the narrower the distribution. In this sense we may name ϵ the evolution hotness. The existence of such a Boltzmann-Gibbs type distribution suggests a global optimization.

There are a few immediate and important conclusions to be drawn here. Near a evolutionary potential maximum, corresponding to the usual Wright evolutionary potential peak, say at $\mathbf{q} = \mathbf{q}_{peak}$, we may expand the potential,

$$\psi(\mathbf{q}) = \psi(\mathbf{q}_{peak}) - (\mathbf{q} - \mathbf{q}_{peak})^\tau U(\mathbf{q} - \mathbf{q}_{peak})/2 + O(|\mathbf{q} - \mathbf{q}_{peak}|^3) . \qquad (7)$$

Here U is a positive definite symmetric matrix as a consequence at the potential peak. The stationary probability density to find the system near this peak is typical Gaussian distribution:

$$\rho(\mathbf{q}, t = \infty) \propto \exp \left\{ -\frac{(\mathbf{q} - \mathbf{q}_{peak})^\tau U(\mathbf{q} - \mathbf{q}_{peak})}{2\epsilon} \right\} . \qquad (8)$$

Thus, away from the potential peak, the probability to find the system will be exponentially small. Such behavior has long been observed in many biological models (12; 23; 24).

One may then wonder about how does the system move from one potential peak to another? This process was first visualized by Wright (83). The relevant mathematical calculation seems to be first performed by Kramers (43). It had been applied to biology (9), where it was shown that the stochastic drive must be involved. Hopping from one potential peak to another must be aided by the stochastic drive. The dominant factor in the hopping rate Γ is usually the difference in potential between the starting peak (peak1) and the highest point (saddle point $\mathbf{q}_{saddle}$) to cross the valley to another peak (9; 43; 77):

$$\Gamma = P_0(A, T, \epsilon, \mathbf{q}_{peak1}, \mathbf{q}_{peak2}, \mathbf{q}_{saddle}) \; \exp\left\{-\frac{\psi(\mathbf{q}_{peak1}) - \psi(\mathbf{q}_{saddle})}{\epsilon}\right\} . \tag{9}$$

This rate can easily be exponentially small when the exponent becomes large. The prefactor P_0 is usually a smooth function of the ascendant matrix A, the transverse matrix T, the numerical constant ϵ, the positions of starting and ending peaks and the saddle. The expressions for P_0 in several cases have been explicitly worked out (43; 77). Eq.(9) is a quantitative measure of robustness and stability. Hence it may explain the usual observation that species are rather stable. Here species are identified with a particular peak. Nevertheless, Eq.(9) implies the possibility of the system to move between peaks when the stochastic drive is finite.

It is already obvious that the shifting balance process visualized by Wright, as summarized by Ewens (23) (*c.f.* subsection II.A), is an apt verbal statement of Eq.(9). We would like to extend this analogy further. The smaller population size and a semi-geological isolated group (deme) used by Wright certainly enhance the hopping rate of the process because of the enhanced fluctuation. Such process has been mathematically carefully studied in physics when discussing the transition from a metastable state to a more stable state: it is energetic very unfavorable to require the whole system makes a transition at the same time; rather, it is more feasible to consider such a transition first occurring locally, in a spatial confined region. Such a process has been called the nucleation process in physics, chemistry, and engineering (45).

We emphasize the important qualitative feature of Eq.(9). The hopping rate between peaks is a combined consequence of both the Wright evolutionary potential ψ, the static landscape if we can neglect its time variation, the stochastic force ξ, and the ascendant matrix A. The measure of the strength of stochastic force, ϵ, is directly appeared in the exponent in Eq.(9) as the scale for the Wright evolutionary potential.

The second law as expressed by Eq.(1) and (2) captures the major features of the evolution dynamics first described by Darwin and Wallace (17), extensively exposed by Darwin (16), and further developed by Fisher, Haldane, Muller, and Wright (67), and by many others (12; 24). It expresses the evolutionary process as a tinkering process (39). In this sense we may also name the second law the law of Darwin. The necessity and chance (57) are represented by the Wright evolutionary potential and the stochastic drive, respectively.

B.   First Law: the Law of Aristotle

The first law reflects the case when there is no stochastic drive in the evolution, i.e., $\epsilon = 0$. This is clearly an approximation, because variation is always there (41), though it may be regarded to be small on a certain scale.

Allowing the stochastic drive be negligible, Eq.(1) becomes

$$[A(\mathbf{q}) + T(\mathbf{q})]\dot{\mathbf{q}} = \nabla\psi(\mathbf{q}) \ . \tag{10}$$

Because of the ascendant matrix A is non-negative, the system will approach the nearest attractor determined by its initial condition, and stay there if already there. Specifically, because $\dot{\mathbf{q}}^\tau A(\mathbf{q})\dot{\mathbf{q}} \geq 0$ and $\dot{\mathbf{q}}^\tau T(\mathbf{q})\dot{\mathbf{q}} = 0$ (eq.(4) and (5)), Eq.(10) leads to

$$\dot{\mathbf{q}} \cdot \nabla\psi(\mathbf{q}) \geq 0 \ . \tag{11}$$

This equation implies that the deterministic dynamics cannot decrease the evolutionary potential: The speed of state variable $\dot{\mathbf{q}}$ points in the same direction as the gradient of the Wright evolutionary potential, $\nabla\psi(\mathbf{q})$. If the ascendant matrix is positive definite, i.e. $\dot{\mathbf{q}}^\tau A(\mathbf{q})\dot{\mathbf{q}} > 0$ for any nonzero $\dot{\mathbf{q}}$, the potential of the system always increases. Hence, the first law clearly states that the system has the ability to find the local adaptive landscape peak represented by the Wright evolutionary potential, determined by the initial condition. However, the shifting between different evolutionary peaks would become impossible in this limit, because the shifting probability vanishes exponentially according to Eq.(9) when $\epsilon \to 0$. We note that Eq.(11) implies that the Wright evolutionary potential is a Lyapunov function in dynamical systems (35).

We have two remarks here. First, from the mathematical theory of dynamical systems, there are in general three types of attractors (35): point, (a)periodic, and chaotic (strange).

The point attractors have been well explored in evolutionary biology since the work of Wright, corresponding to the Wright evolutionary potential maxima. Other two types of attractors have also been observed in biology (1; 38; 51; 58). The periodic attractor or the limit cycle in population genetics (1; 38) will be explicitly discussed in section V. For point attractors, the transverse matrix can be zero. Then the ascendant route to the potential maximum would follow the most rapid ascendant path in the landscape defined by the Wright evolutionary potential. For other two kinds of attractors, the transverse matrix cannot be zero.

If we further assume the ascendant matrix $A = 0$ in Eq.(10), the evolutionary dynamics will not change the system's evolutionary potential, hence it is completely conservative. This is precisely what can be obtained from the Newtonian dynamics (30): Energy is conserved in Newtonian dynamics. Here we tentatively denote the conservative dynamics as the Newtonian dynamics: the Newtonian dynamics can be casted into the form of

$$T(\mathbf{q})\dot{\mathbf{q}} = \nabla \psi(\mathbf{q}) \ . \tag{12}$$

This leads to our second remark: Based on this consideration one may be inclined to conclude that Newtonian dynamics is a special case of the Darwinian dynamics as expressed by Eq.(1) and (2), the case of vanishing ascendant matrix, $A = 0$, and zero stochastic drive, $\xi = 0$. Many biologists may consider this conclusion natural (19; 53).

The tendency implied in Eq.(10) to approach a fixed point (equilibrium) and to remain there has been amply discussed by Aristotle (8), well known in both physics and biology. The periodic motion might have been known in the classical Greek time, but the concept of strange attractor was certainly foreign to Aristotle. Nevertheless, to capture this tendency to an attractor when $\epsilon = 0$,

$$\mathbf{q} \to \mathbf{q}_{attractor} \ , \quad t \to \infty \ , \tag{13}$$

and the ability to remain there we may call Eq.(10) the law of Aristotle. It is evident that in the present setting the first law is mathematically a special case of the second law. This law does give us a necessary reference point to define species and other relevant quantities in a clean manner, if stochasticity could be ignored.

Two comments are in order to avoid a possible misinterpretation. As emphasized above, only the meaning of approaching to stable fixed point has been used in naming Eq.(10) the law of Aristotle. Our first comment is that the conservative part of dynamics was not

understood by Aristotle. The most clear manifestation of the conservative dynamics was the inertial law, first formulated by Newton as his first law of motion in physics, which started the modern science. The second comment is that, though we assume it to be zero in Eq.(10), the fluctuation or stochasticity is important. We postulated it in Eq.(2) that the ascendancy matrix A is connected to the stochastic drive ξ. It was Darwin who first fully recognized the importance of the fluctuation in biological evolution, hence the origin and change of species. Those concepts were not at all appreciated by Aristotle.

C. Third Law: the Law of Hierarchy

The third law is a relationship law. It allows us to define the connection of the focused (mesoscopic, for a convenient description) level of description to its lower (microscopic) and higher (macroscopic) ones. For example, there exists at least three large subfields in biology which mutually influence each other: ecological dynamics (51; 74), population genetics (23; 55), the focus of the present review, and dynamics of gene regulatory networks (56; 85; 86). Each subfield may have its own mathematical equations but it is certainly not isolated from others. For example, all those dynamics are manifested through the behaviors of each individual organism of the species. Dynamically, each have its own characteristic time scale: Ecology in terms of populations of species may be slow, involving many generations. The continuous description of population genetics also requires a time span over many generations. The dynamics of gene regulatory networks is fast, since it can occur within one generation.

Confining our attention to population genetics, how to make the connection between the discrete dynamics, the micro level, to the continuous dynamics, the focused level, is the content of the third law. It may be stated as follows: The Wright evolutionary potential $\psi(\mathbf{q})$ has the contribution from lower level in terms of time average on the time scale of the observation and description–the level of the present focus, the contribution from the interaction among various components of the focused level, and the contribution from the higher level. The stochastic drive $\xi(\mathbf{q}, t)$ is the remainder of all those contributions whose dynamics is fast on the interested time scale at focused level. Hence its time average is zero. This stochastic contribution may be either unknown from microscopic (lower) and mesoscopic and macroscopic (focused and higher) levels or unnecessary to be specified in

details. Only its probability distribution is needed and is approximated by a Gaussian distribution in the present article. The stochastic drive determines the ascendant matrix $A(\mathbf{q})$, and the transverse matrix $T(\mathbf{q})$ should be further determined by the dynamics of the system.

The lower, or microscopic, level contribution to the Wright evolutionary potential $\psi(\mathbf{q})$ and the stochastic drive $\xi(\mathbf{q}, t)$ may allow us to compute the intrinsic adaptive landscape and the intrinsic source of evolution. However, historically the computation of this contribution tends to neglect the horizontal interaction, the interaction among different populations at the same level of description, which is usually nonlinear. On the other hand, the same and higher level contributions may suggest that a control mechanism, such as a feedback, may be from all three levels. The combination of all three of them suggests that the evolution is nonlinear, asymmetric, mutually interactive, stochastic, and may be controllable.

There is a degree of uncertainty and arbitrariness in both the assignment of different levels of descriptions and the dichotomy of deterministic and stochastic terms in Eq.(1). This dilemma has been amply discussed in both physical (66; 77) and biological (47; 75) sciences. This has also been reflected in the mathematical theory of stochastic process. Our way to solve this problem will be proposed as the zero mass limit in next section in connection to usual dynamics, which is different from both Ito and Stratonovich approaches and may be interpreted as an indication of the richness of the hierarchical structure. The law of the hierarchy requires that the specification to carrying the analysis of the stochastic differential equation is needed. Without any such specification, the Eq.(1) and (2) would be the *pre*-equations as discussed by van Kampen (77).

The third law is a reflection of the hierarchical structure of the whole dynamics. The essence of this law is to acknowledge the existence of multiple time scales: the mesoscopic time scale with which we observe the system dynamics at the focused level of description and the micro time scale with which fine structures and microscopic dynamics come into play. The microscopic time scale can be regarded as zero in a specific sense.

D. F-Theorem

In his classic treatise on genetical foundation of evolution (25), Fisher stated his fundamental theory of natural selection (FTNS): *The rate of increase in fitness of any organism*

at any time is equal to its genetic variance in fitness at that time. This statement connects two opposite processes: the process towards the maximum and the process of variation.

Fisher noticed a profound similarity between FTNS and the second law of thermodynamics (25):

"Both are properties of population, or aggregates, true irrespective of the nature of the units which compose them; both are statistical laws; each requires the constant increase of a measurable quantity, in the one case the entropy of a physical system and in the other the fitness, measured by m, of a biological population. As in the physical world we can conceive of theoretical systems in which dissipative forces are wholly absent, and in which the entropy consequently remains constant, so we can conceive, though we need not expect to find, biological populations in which the genetic variance is absolutely zero."

His last statement corresponds nicely to the discussion of the first law in subsection III.B. He likened FTNS to the second law of thermodynamics, and suggested that it "should hold the supreme position among the biological sciences".

Nevertheless, Fisher also noticed five troubling differences (25), or the exceptions as later called by Gould (32):

"(1) The systems considered in thermodynamics are permanent; species on the contrary are liable to extinction, although biological improvement must be expected to occur up to the end of their existence.

(2) Fitness, although measured by a uniform method, is qualitatively different for every different organism, whereas entropy, like temperature, is taken to have the same meaning for all physical systems.

(3) Fitness may be increased or decreased by changes in the environment, without reacting quantitatively upon that environment.

(4) Entropy changes are exceptional in the physical world in being irreversible, while irreversible evolutionary changes form no exception among biological phenomena. Finally,

(5) entropy changes lead to a progressive disorganization of the physical world, at least from the human standpoint of utilization of energy, while evolutionary changes are generally recognized as producing progressively higher organization in the organic world."

In the present formulation, we notice that the stochasticity-ascendancy relation, Eq.(2), is similar to a fluctuation-dissipation theorem (FDT) in physics and chemistry (60; 84). FDT may be verbally stated as follows (44): *The same processes that drive fluctuations in*

the neighborhood of a typical equilibrium or steady state configuration also drive the configuration back towards a typical equilibrium when it is displaced from equilibrium. This is one of the most important results in nonequilibrium processes. There is a striking similarity between FTNS and FDT in that the approach to equilibrium is driven by the fluctuations or variations. Both FTNS and FDT imply that the return to the evolutionary potential peak and the fluctuation from the peak are governed by the same process. Thus, correct interpretation of FTNS should be dynamical in nature, not thermodynamic. Hence we should replace the fitness in Fisher's statement by the Wright evolutionary potential. In addition, we note that the fitness should not correspond to entropy as Fisher did. Nor should one relate FTNS to the second law of thermodynamics. Instead, FTNS should correspond to the stochasticity-ascendancy relation, Eq.(2), an FDT in physics and chemistry.

With this interpretation of FTNS as FDT, the five exceptions to FTNS listed by Fisher as quoted above disappear: Since the Wright evolutionary potential is not entropy, there is no comparison to the entropy in the physical world, the exception (4) and (5) immediately become irrelevant. In fact, a nice demonstration on the difference between biology and physics had been done by Schrödinger (69), encoded in his phrase "negative entropy". The biological systems are open, comparing with the close systems where the second law of thermodynamics applies. This important observation has been formulated quantitatively and in detail by Prigogine in his dissipative structure (59).

As indicated by works in population genetics (47; 75), a consideration over many generations is needed to establish the continuous representation, a manifestation of the third law. The situation described in exception (1) has been precisely taken care of. Since the Wright evolutionary potential is not entropy, and since it is defined for each situations, the exception (2) is gone. In addition, the Wright evolutionary potential is a relative concept, there is no meaning to assign an absolute potential value. It is also a local and individual concept. Instead, entropy has an absolute value and is global in nature. Because the evolutionary potential can only be defined through a reference point, if the environment of a species is changed, even though its immediate biological consequence is not clear, its evolutionary potential is changed. Hence, the exception (3) does not apply in the present formulation.

It should be kept in mind that the attention should not be dwelled too much on Fisher's exact wording: He formulated FTNS before the general formulation of FDT in physics and

chemistry and his formulation was close to the modern one: FDT has been indeed regarded as a dynamical manifestation of the second law of thermodynamics. In the present reformulation, FTNS represents a remarkable insight: It immediately connects the adaptation to the stochastic drive for the motion in the adaptive landscape defined by the Wright evolutionary potential.

We return to Fisher's original content of FTNS. If the populations remain fixed and if the state variables are instead the genetic variables, the variations in Eq.(2) should indeed be the additive genetic variations. Even in this situation we should emphasize that the Eq.(2) is independent of the Wright evolutionary potential. This independence is the indication of its fundamental importance. For example, if there is no selection by fitness, that is, if the Wright evolutionary potential is a constant, the system would diffuse over the whole state space in search of the largest and simple connected volume in hyperspace according to FTNS, such as in the case of holey adaptive landscape model for speciation (28). This suggests that the *the rate of increase* used in Fisher's statement is not precise, which may only be true near a potential maximum. In general, it is the diffusion matrix which associates with the stochasticity in the conventional formulation to be discussed in next section. We will make this point more concrete in section VI.

As implied in the first law, the ascendancy of the system is described by the ascendant matrix A, which in turn is completely determined by the stochastic drive ξ according to the stochasticity-ascendancy relation, Eq.(2). The discussion following Eq.(9) indicates that the ability of the system to find a better evolutionary potential maximum, not only the nearest local maximum, or, to reach the global equilibrium, is guaranteed by the stochastic drive. This suggests that Eq.(2) is a statement on the unification of the two completely opposite tendencies: adaptation and optimization.

It is interesting to point out that even this unification of ascendancy and stochastic effect had not been completely brought out by Fisher. Without the stochastic drive in the dynamics equation, we are effectively dealing with Eq.(10), the first law in the present formulation. Therefore, the evolution would eventually lead to the highest local peak, and would stay there. Mathematically, this implies that eventually $\dot{\mathbf{q}}(t \to \infty) = 0$, a fact which is in clear contradiction to observations. Fisher apparently recognized this difficulty. He did it away with the continuous changing of his fitness by 'deterioration of the environment' (25), which does not completely agree with observations either, though it is more difficult to

be tested by observations. In the light of the present formulation, the including of stochastic drive into the dynamics equation makes the introduction of 'deterioration of the environment' completely unnecessary. There is a dynamical balance right at the evolutionary potential peak as described by Eq.(1) and (2).

Ever since Fisher's proposal of the fundamental theorem of natural selection, misrepresentation and misunderstanding have been associated with this insightful statement, as discussed by Crow (15) and Grafen (33). Though Fisher might have confined his discussion within genetic variations, the comparison of Fisher's statement to Eq.(2) displays a remarkable similarity. We emphasize again that on the left hand side of Eq.(2) is the measure of the variations, which should include all variations affecting the evolutionary dynamics, including the additive genetic variation, and on the right hand side may be interpreted as the rate to the peak of the Wright evolutionary potential, with a proper choice of units. Hence, we may also call Eq.(2) the fundamental theorem of evolution, as a tribute to Fisher's great insight, or the Fisher's theorem. Due to its similarity to the fluctuation-dissipation theorem in physics, we may simply name Eq.(2) the F-Theorem for short, to incorporate all related meanings. Its importance is evident: It is an integral part of the second law of evolution, the Darwinian dynamics. It enables the system to find the global evolutionary potential maximum. It should be pointed out again that the F-Theorem in the present formulation is independent of the Wright evolutionary potential: It exists even if the Wright evolutionary potential is a constant. By generalization the variation beyond genetic ones, this fundamental theorem can be also used in other parts of biology, for example, developmental biology and ecology.

A note on the semantics is in order. We have named Eq.(2) the F-Theorem in the present subsection, in connection to fundamental theorem of natural section and to fluctuation-dissipation theorem. In strict mathematical sense this is inappropriate: Eq.(2) has been introduced in the present article as a part of a postulate. It is a part of an axiom, not a derived result in the present formulation. Nevertheless, just like in the case of the fluctuation-dissipation theorem we believe that the F-Theorem may be derivable from a more fundamental description and the word "theorem" is used here in this sense. For the F-Theorem in the context of population genetics we nevertheless are not aware of any such derivation. For the derivation of fluctuation-dissipation theorem in physics and chemistry, we suggests the interesting readers to Ref.[(27)] and [(22)] for a taste of the difficulty, where its mathematically

rigorous justification is an ongoing research program.

IV. CLASSICAL FORMULATIONS

The purpose of this section is to demonstrate that the three laws proposed in section II are in fact deeply rooted in the classical formulations of evolutionary dynamics. It will reveal, particularly in subsection IV.A, that a conservative dynamics represented by the transverse T is needed to unify ideas from Wright and Fisher. This conservative dynamics has been overlooked in the study of evolutionary dynamics. The demonstration of the equivalence below also provides a procedure, not necessarily easy in mathematics and in computation, to compute the Wright evolutionary potential, the ascendant and transverse matrices from classical formulations.

It is known that there are several standpoints to study the dynamics. One focuses on the trajectory of state variables as function of time, Newton's three laws on dynamics are such example. Another focuses on the distribution of state variable, such as the Liouville formulation of classical dynamics in physics (30). Both are equivalent and complementary to each other. There is a third standpoint, the discrete description of dynamics, which can be connected to either of above standpoints and will not be pursued in the present article. For such a connection we refer readers to the commentated collected papers in population genetics (47) and an insightful paper in physical sciences (49). The previous approach from either the system's trajectory in state space or the evolution of probability distribution function point of view will be tentatively named the classical formulation.

A. Standard Stochastic Differential Equation

Now we make the connection between the dynamics described by Eq.(1) and (2) and the dynamical equations typically encountered in evolution. We start with the standard stochastic differential equation widely used in mathematical literature (75; 77):

$$\dot{\mathbf{q}} = \mathbf{f}(\mathbf{q}) + \zeta(\mathbf{q}, t) \ . \tag{14}$$

Here $\mathbf{f}(\mathbf{q})$ is the deterministic nonlinear drive of the system, which includes effects from both other components and itself. The stochastic drive is $\zeta(\mathbf{q}, t)$, which differs from ξ in Eq.(1)

in appearance but both are governed by the same dynamics. For simplicity we will assume that **f** is a smooth function whenever needed. Without loss of generality the stochastic drive in Eq.(14) is assumed to be Gaussian and white with the variance,

$$\langle \zeta(\mathbf{q}, t)\zeta^{\tau}(\mathbf{q}, t')\rangle = 2D(\mathbf{q}) \, \epsilon \, \delta(t - t'), \tag{15}$$

and zero mean, $\langle \zeta(\mathbf{q}, t)\rangle = 0$. Eq.(9) is consistent with Eq.(2), Gaussian white noise and same dynamical origin. Again here $\langle ...\rangle$ indicates the average with respect to the dynamics of the stochastic drive ζ, not over the state variable $\mathbf{q}$. According to the biology convention the positive semi-definite symmetric matrix $D = \{D_{ij}\}$, with $i, j = 1, 2, ..., n$, is the diffusion matrix.

Both the divergence and the skew matrix of the nonlinear drive **f** are in general non-zero:

$$\nabla \cdot \mathbf{f} \neq 0 , \tag{16}$$

$$\nabla \times \mathbf{f} \neq 0 . \tag{17}$$

Here the divergence is explicitly $\nabla \cdot \mathbf{f} = \sum_{j=1}^{n} \partial f_j / \partial q_j = tr(S)$, and the skew matrix $\nabla \times \mathbf{f}$ is twice the anti-symmetric part of the selection matrix S: $(\nabla \times \mathbf{f})_{ij} = S_{ji} - S_{ij}$, with

$$S_{ij} = \frac{\partial f_i}{\partial q_j} , \; i, j = 1, 2, ..., n . \tag{18}$$

Since the divergence is non-zero the state space volume is not conserved, leading to ascendancy. The skew matrix is again non-zero, or putting it differently the selection matrix S is asymmetric. This implies the existence of the transverse matrix T.

A note on notation is in order: In the classical formulations (23) the diagonal part of D is called variance, also called the diffusion coefficients, and the off-diagonal part of D is called covariance. Mathematically, a coordinate transformation exists that diagonalizes the matrix D, hence turns D into diffusion coefficients in the new coordinate representation. To simultaneously maintain the general expression for D and to keep the meaning of diffusion, we here name the whole matrix D as the diffusion matrix. The diffusion matrix D is in general a function of state variable and time.

Now, we give an explicit construction which demonstrates the connection between Eqs.(1,2) and Eqs.(14,15). Assume that both Eq.(1) and (14) describe the same dynamics. The speed $\dot{\mathbf{q}}$ is then the same in both equations. The connection from Eq.(1) to (14)

is straightforward: Multiplying both sides of Eq.(1) by $[A(\mathbf{q}) + T(\mathbf{q})]^{-1}$ leads to Eq.(14). Converting Eq.(14) into (1) is mathematically more involved.

Using Eq.(14) to eliminate the speed $\dot{\mathbf{q}}$ in state space in Eq.(1), we have

$$[A(\mathbf{q}) + T(\mathbf{q})][\mathbf{f}(\mathbf{q}) + \zeta(\mathbf{q}, t)] = \nabla\psi(\mathbf{q}) + \xi(\mathbf{q}, t) \ .$$

The dynamics of stochastic drive is different from that of the state variable. This is expressed in Eq.(2) or (15) in that the average is not on state variable. This is also in consistent with the third law: the stochastic dynamics is from a different level. Thus, the stochastic drive and the state variable can be regarded as independent variables. This suggests following two equations

$$[A(\mathbf{q}) + T(\mathbf{q})]\mathbf{f}(\mathbf{q}) = \nabla\psi(\mathbf{q}) \ , \tag{19}$$

and

$$[A(\mathbf{q}) + T(\mathbf{q})]\zeta(\mathbf{q}, t) = \xi(\mathbf{q}, t) \ . \tag{20}$$

Those two equations suggest a rotation in state space.

Multiplying Eq.(20) by its own transpose on each side and averaging over the stochastic drive, we have

$$[A(\mathbf{q}) + T(\mathbf{q})]D(\mathbf{q})[A(\mathbf{q}) - T(\mathbf{q})] = A(\mathbf{q}) \ . \tag{21}$$

In obtaining Eq.(21) we have also used Eq.(2) and (15). Eq.(21) suggests a duality between the standard stochastic differential equations and Eq.(1): A large ascendant matrix A implies a small diffusion matrix D when the transverse matrix T is small. In the opposite limit of large transverse matrix T, the diffusion matrix D is proportional to the ascendant matrix A. It is a generalization of the Einstein relation (20; 77) to nonzero transverse matrix.

Next we introduce an auxiliary matrix function G for a better connection to the classical formulation, defined as

$$G(\mathbf{q}) = [A(\mathbf{q}) + T(\mathbf{q})]^{-1} \ . \tag{22}$$

Here '-1' indicates the matrix inversion. Such an auxiliary function bring out a close relationship between the presentation formulation and those of classical ones. In particular, the role of variance in the classical formulations, the diffusion matrix D, has a straightforward meaning in G, exemplified by Eq.(27) below.

Using the property of the Wright evolutionary potential ψ:

$$\nabla \times \nabla\psi = 0 \tag{23}$$

$[(\nabla \times \nabla)_{ij} = \nabla_i \nabla_j - \nabla_j \nabla_i = \partial^2/\partial q_i \partial q_j - \partial^2/\partial q_j \partial q_i \; , i,j = 1,2,...,n \;]$, Eq.(19) leads to

$$\nabla \times [G^{-1}\mathbf{f}(\mathbf{q})] = 0 \; , \tag{24}$$

which gives $n(n-1)/2$ conditions.

Note that

$$
\begin{aligned}
A(\mathbf{q}) &= \frac{1}{2}[(A(\mathbf{q}) + T(\mathbf{q})) + (A(\mathbf{q}) + T(\mathbf{q}))^\tau] \\
&= \frac{1}{2}[G^{-1} + (G^\tau)^{-1}] \; ,
\end{aligned}
\tag{25}
$$

and that the generalized Einstein relation, Eq.(21), can be rewritten as

$$G^{-1}D(G^\tau)^{-1} = \frac{1}{2}[G^{-1} + (G^\tau)^{-1}] \; , \tag{26}$$

we have thus the following equation

$$G + G^\tau = 2D \; , \tag{27}$$

which readily determines the symmetric part of the auxiliary matrix G, another $n(n+1)/2$ conditions. Eq.(24) and (27) form a complete set of equations: The total number of equations embedded in them is n^2, precisely the number to determine the auxiliary matrix G. Hence, with an appropriate boundary condition, G can be found, so will be A, T, and ψ. A gradient expansion scheme to solve Eqs.(24,27) is presented below, which emphasizes the role played by fixed points: It is exact near fixed points.

The auxiliary function G may be formally solved as an iteration in gradient expansion:

$$G = D + Q \; , \tag{28}$$

with

$$
\begin{aligned}
Q &= \lim_{j \to \infty} \Delta G_j \; , & (29) \\
\Delta G_j &= \sum_{l=1}^{\infty} (-1)^l [(S^\tau)^l \tilde{D}_j S^{-l} + (S^\tau)^{-l} \tilde{D}_j S^l] \; , & (30) \\
\tilde{D}_0 &= DS - S^\tau D \; , & (31) \\
\tilde{D}_{j \geq 1} &= (D + \Delta G_{j-1}) \left\{ [\nabla \times (D^{-1} + \Delta G_{j-1}^{-1})]\mathbf{f} \right\} (D - \Delta G_{j-1}) \; . & (32)
\end{aligned}
$$

At each step of solving for ΔG_j only linear algebraic equation is involved. One can verify that the matrix Q is anti-symmetric. For a simple case a formal solution of such algebraic

equation was given in (3), and an explicit procedure was found for generic cases in (44). Eqs.(29-32) are the result of a local approximation scheme: If the selection matrix S and the diffusion matrix D are constant in space, the exact solution only contains the lowest order contribution in the gradient expansion: $Q = \Delta G_j = \Delta G_0$. We regard Eqs.(29-32) as the biological solution to Eq.(24) and (27), because it preserves all the fixed points of deterministic drive $\mathbf{f}$. The connection from Eq.(14) to (1) is therefore uniquely determined:

$$
\begin{cases}
\psi(\mathbf{q}) & = \int_C d\mathbf{q}' \cdot [G^{-1}(\mathbf{q}')\mathbf{f}(\mathbf{q}')] \\
A(\mathbf{q}) & = [G^{-1}(\mathbf{q}) + (G^\tau)^{-1}(\mathbf{q})]/2 \\
T(\mathbf{q}) & = [G^{-1}(\mathbf{q}) - (G^\tau)^{-1}(\mathbf{q})]/2
\end{cases} .
\tag{33}
$$

Here the sufficient condition $\det(A + T) \neq 0$ is used, and the end and initial points of the integration contour C are $\mathbf{q}$ and $\mathbf{q}_0$ respectively.

We point out that in the limit of vanishing strength of stochastic drive, i.e., $\epsilon = 0$ in Eq.(2) and (15), the above connection remains unchanged.

B. Fokker-Planck Equation

In experimental studies in biology, we are often interested in the distribution of the state variable versus time rather than focusing on the individual trajectory of the system. This is especially true in population genetics where one almost exclusively deals with distribution. This implies that either there is an ensemble of identical systems or repetitive experiments are carried out. To describe this situation, we need a dynamical equation for the distribution function in the phase space. This goal can be accomplished by the so-called Fokker-Planck equation, or the diffusion equation, or the Kolmogorov equation (12; 23; 47; 66; 77).

In this subsection, a new procedure is presented to find the equation of the distribution function. It is motivated from a theoretical physics point of view. This procedure will establish that the Wright evolutionary potential ψ in Eq.(1) indeed plays the role of potential energy in physics in the manner envisioned by Wright: the adaptive landscape is quantified by the evolutionary potential and the steady state distribution is given by Eq.(6). The system indeed tends to stay at the peaks of evolutionary potential as suggested by the distribution function. Our starting point will be the second law, Eq.(1), not the standard stochastic differential equation, Eq.(14), or a master equation from which most previous derivations in population genetics started (23).

The existence of both the deterministic and the stochastic drives in Eq.(1) suggests that there are two well separated time scales in the system: the microscopic or fine time scale to describe the stochastic drive and the macroscopic or course time scale to describe the system motion. The former time scale is much smaller than the latter. This separation of time scales further suggests that the macroscopic motion of the system has "inertial": it cannot response instantaneously to the microscopic motion. To capture this feature, we introduce a small constant inertial "mass" m (no confusion with the m used by Fisher) and a kinetic momentum vector $\mathbf{p}$ for the system. Our state space is then enlarged: it is now a $2n$-dimensional space. The dynamical equation for the system takes the form:

$$\dot{\mathbf{q}} = \frac{\mathbf{p}}{m} , \tag{34}$$

which defines the kinetic momentum, and

$$\dot{\mathbf{p}} = -[A(\mathbf{q}) + T(\mathbf{q})]\frac{\mathbf{p}}{m} + \nabla\psi(\mathbf{q}) + \xi(\mathbf{q}, t) , \tag{35}$$

which is the extension of Eq.(1): In the limit $m \to 0$ we recover Eq.(1) (c.f. below). We note that the ascendant matrix A and the stochastic drive are independent of the kinetic momentum $\mathbf{p}$. The Fokker-Planck equation in this enlarged state space can be immediately obtained (77):

$$\left\{\partial_t + \frac{\mathbf{p}}{m}\cdot\nabla_{\mathbf{q}} + \bar{\mathbf{f}}\cdot\nabla_{\mathbf{p}} - \nabla_{\mathbf{p}}^\tau A\left[\frac{\mathbf{p}}{m} + \nabla_{\mathbf{p}}\right]\right\}\rho(\mathbf{q}, \mathbf{p}, t) = 0 . \tag{36}$$

Here

$$\bar{\mathbf{f}} = \frac{\mathbf{p}^\tau T}{m} + \nabla_{\mathbf{q}}\psi , \tag{37}$$

and t, $\mathbf{q}$, and $\mathbf{p}$ are independent variables. The subscripts of ∂ and ∇ indicate the differentiation with respect to the indicated. The stationary distribution can be found and easily verified, when the Wright evolutionary potential is bounded above and normalizable, as (77)

$$\rho(\mathbf{q}, \mathbf{p}, t = \infty) = \frac{1}{\mathcal{Z}}\exp\left\{-\frac{\mathbf{p}^2/2m - \psi(\mathbf{q})}{\epsilon}\right\} , \tag{38}$$

with $\mathcal{Z} = \int \prod_{i=1}^n dq_i \prod_{i=1}^n dp_i \exp\{-[\mathbf{p}^2/2m - \psi(\mathbf{q})]/\epsilon\}$ the partition function in the extended state space. There is an explicit separation of state variable and its kinetic momentum in Eq.(38). The elimination of the momentum in the small mass limit will not affect this distribution. Hence, Eq.(38) confirms that the expected Boltzmann-Gibbs distribution, Eq.(6) from the Eq.(1) and (2), is the right distribution function.

We proceed to outline the procedure to find the Fokker-Planck equation corresponding to Eq.(1) and (2) without the kinetic momentum $\mathbf{p}$. We first illustrate how to recover Eq.(1) from Eq.(34) and (35). In the limit of $m \to 0$, the fast dynamics of kinetic momentum $\mathbf{p}$ always follows the motion of the state variable $\mathbf{q}$ whose dynamics is slow. Hence we may set $\dot{\mathbf{p}} = 0$ in Eq.(35) and replace the kinetic momentum using Eq.(34), which is then Eq.(1) after moving the speed to the left-side of equation. For the Fokker-Planck equation, the explicit separation of the kinetic momentum and state variable in the stationary distribution gives the guidance on the procedure: The resulting Fokker-Planck equation must be able to reproduce this feature. The Fokker-Planck equation is then found as

$$\partial_t \rho(\mathbf{q}, t) = \nabla^\tau [-\mathbf{f}(\mathbf{q}) - \Delta \mathbf{f}(\mathbf{q}) + D(\mathbf{q})\nabla]\rho(\mathbf{q}, t) , \tag{39}$$

with $\Delta \mathbf{f}$ the solution of the equation

$$\nabla \cdot \Delta \mathbf{f} + \Delta \mathbf{f} \cdot \nabla \psi - \nabla \cdot [GTG^\tau \nabla \psi] = 0 . \tag{40}$$

If the probability current density is defined as

$$\mathbf{j}(\mathbf{q}, t) \equiv (\mathbf{f} + \Delta \mathbf{f} - D\nabla)\rho(\mathbf{q}, t) , \tag{41}$$

the Fokker-Planck equation is a statement of the probability continuity:

$$\partial_t \rho(\mathbf{q}, t) + \nabla \cdot \mathbf{j}(\mathbf{q}, t) = 0 . \tag{42}$$

In population genetics equations in the form of Eq.(39) or (42) have been routinely and successively employed (12; 23; 24; 47). The stationary state corresponds to the condition $\nabla \cdot \mathbf{j}(\mathbf{q}, t = \infty) = 0$. One may verify that the stationary distribution $\rho(\mathbf{q}, t = \infty)$ in Eq.(6) is indeed the time independent solution of the Fokker-Planck equation: The stationary probability current

$$\mathbf{j}(\mathbf{q}, t = \infty) = (GTG^\tau + \Delta \mathbf{f})\nabla \psi(\mathbf{q}) \, \rho(\mathbf{q}, t = \infty) , \tag{43}$$

and $\nabla \cdot \mathbf{j}(\mathbf{q}, t = \infty) = 0$.

The connection between the standard stochastic differential equation and Fokker-Planck equation has been under intensive study by biologists, physicists, chemists, mathematicians, and others over last 70 years (12; 24; 47; 77). However, there exists an ambiguity for the generic nonlinear situation (75; 77). We attribute this ambiguity to the asymptotic nature

of the connection in which a procedure must be explicitly defined: Different procedures will in general lead to different results. Biologically, it is a statement on how the dichotomy of deterministic and stochastic drives is done, a genuine indication of the hierarchical nature of the dynamics. What has been demonstrated in this subsection is one way of carrying out this procedure:

$$m \to 0 \ . \tag{44}$$

Mathematically, we have now demonstrated the equivalency between Eq.(1) and (2) and the classical formulations in terms Eq.(14) and (15) or Eq.(39): there indeed exist evolutionary potential, the ascendant matrix, and the transverse matrix. The hierarchical structure is represented by the zero mass limit $m \to 0$. The four dynamical components are all mixed up in the classical formulation of Eq.(14) and (15). For the classical formulation represented by eq.(39) or (42), not only four dynamical components are mixed, the zero mass limit is also needed. Hence Eq.(39) or (42) effectively encodes all the three laws postulated in section III. From Eq.(1) and (2) to Eq.(14) and (15) it is straight forward: involving only algebraic manipulation. The converse is in general not easy: the task to explicitly construct the evolutionary potential from either Eq.(14) and (15) to Eq.(1) and (2) involving solving first order partial differential equation with appropriate boundary conditions. This difficulty has been encountered in previous attempts and is the reason that there are only limited successes (14; 59). In the next section, section V, a nontrivial example will be explicitly discussed.

There is a question of the meanings of kinetic momentum p and the mass m. Their meanings in classical physics are well defined and will not be elaborated here. We refer readers to Ref.[(30)] for an authoritative discussion. However, it is not at all clear what are their precise meanings in population genetics. They have been used here as mathematical devices to make the connection between the present formulation of Eq.(1) and (2) to the classical formulations and to show that the evolutionary potential and other quantities do exist. They are also used as a way to realize the hierarchical structure in population genetics. In the end they do not explicitly appear in dynamical equations. Whether or not they have deeper meanings in population genetics in particular and in biology in general remains to be explored (*c.f.* subsection VII.C.).

C. Detailed Balance Condition

There is an important class of evolution dynamics in which the anti-symmetric matrix $Q = 0$. Under this condition, the transverse matrix $T = 0$, and $\Delta \mathbf{f} = 0$. The Fokker-Planck equation becomes

$$\partial_t \rho(\mathbf{q}, t) = \nabla^\tau [-\mathbf{f}(\mathbf{q})) + D(\mathbf{q})\nabla] \rho(\mathbf{q}, t) , \tag{45}$$

and the stationary probability current is everywhere zero in state phase:

$$\mathbf{j}(\mathbf{q}, t = \infty) = 0 . \tag{46}$$

In this situation one finds that

$$\nabla \psi(\mathbf{q}) = D^{-1}(\mathbf{q})\mathbf{f}(\mathbf{q}) , \tag{47}$$

$$A = D^{-1} . \tag{48}$$

The Wright evolutionary potential and the connection between Eq.(1) and the standard stochastic differential equation can be directly read out from equations. This is the well-known symmetric dynamics in biological (12; 24; 47) and physical (77) sciences. A condition to generate this kind of equilibrium state in biology was first noticed, in retrospective, by Hardy (37) and Weinberg (80). This zero probability current condition is the usual detailed balance condition.

D. More on the Third Law

We may further illustrate the third law. In reaching Eq.(39) we have taken a specific way to classify the stochastic and deterministic drives, the zero "mass" limit, $m \to 0$. We mentioned in subsection III.C that there are other ways to do this classification. Two of them are particularly well known in physical and biological sciences, Ito and Stratonovich. Starting from Eq.(14) an d(15), the Fokker-Planck equation according to Ito's prescription is (77)

$$\partial_t \rho(\mathbf{q}, t) = \nabla^\tau [-\mathbf{f}(\mathbf{q}) - \Delta \mathbf{f}_{Ito}(\mathbf{q}) + D(\mathbf{q})\nabla] \rho(\mathbf{q}, t) , \quad (Ito) \tag{49}$$

and the i-th component of correction $\Delta \mathbf{f}_{Ito}(\mathbf{q})$

$$\Delta f_{Ito,i}(\mathbf{q}) = - \sum_{j=1}^{n} \nabla_j D_{ij}(\mathbf{q}) . \tag{50}$$

Starting from Eq.(14) and (15), the Fokker-Planck equation according to Stratonovich's prescription is (77)

$$\partial_t \rho(\mathbf{q}, t) = \nabla^\tau [-\mathbf{f}(\mathbf{q}) - \Delta \mathbf{f}_{Str}(\mathbf{q}) + D(\mathbf{q})\nabla]\rho(\mathbf{q}, t) , \quad (Str) \tag{51}$$

and the i-th component of correction $\Delta \mathbf{f}_{Str}(\mathbf{q})$

$$\Delta f_{Str,i}(\mathbf{q}) = -\sum_{j,l=1}^{n} d_{il}(\mathbf{q})\nabla_j d_{jl}(\mathbf{q}) . \tag{52}$$

Here we have rewritten the standard stochastic differential equation, Eq.(14), in the form

$$\dot{\mathbf{q}} = \mathbf{f}(\mathbf{q}) + d(\mathbf{q})\hat{\zeta}(t) , \tag{53}$$

with $d(\mathbf{q})$ is a smooth $n \times n$ matrix function of $\mathbf{q}$ to remove the state variable dependence from the noise $\zeta(\mathbf{q}, t)$,

$$D(\mathbf{q}) = d(\mathbf{q})d^\tau(\mathbf{q}) , \tag{54}$$

$$\langle \hat{\zeta}_i(t)\hat{\zeta}_j(t')\rangle = 2\delta_{ij}\delta(t - t') , \tag{55}$$

and $\langle \hat{\zeta} \rangle = 0$,

Eq.(39), (49), and (51) are all different from each other. The major difference lies in the deterministic driving force $\mathbf{f}$: after a proper re-definition of driving force they all can be rewritten in the form of Eq.(39) with different $\Delta \mathbf{f}(\mathbf{q})$ and different $\mathbf{f}$ to correspond back to Eq.(1) and (2). Such a mathematical reconstruction is similar to the Legendre transformation in thermodynamics and will be explored elsewhere. Those equations, Eq.(39), (49), and (51), suggest that in reaching Eq.(39), the third law postulated in section III is necessary.

It is evident that all four dynamical elements are implicitly included in Eq.(39). Starting from Eq.(39), in order to reconstruct the four dynamical elements, we may need to find the corresponding Eq.(14) and (15) first. Then using Eq.(24) and (27) for a further reconstruction to obtain Eq.(1) and (2). This suggests that the Wright's evolutionary potential always exists, contrast to the negative claim in literature (65). Examples of such reconstruction can be found in Ref.[(44)] for fixed points and in next section for a limit cycle dynamics.

V. EVOLUTIONARY POTENTIAL AND LIMIT CYCLE DYNAMICS

In this section we discuss an intriguing case of co-existence of limit cycle dynamics and the evolutionary potential. The limit cycle dynamics exists in biological fields, ecology (58; 74),

population genetics (1; 38; 65), or gene regulatory networks (56; 59). The existence of evolutionary potential in population genetics has been questioned because of a perceived absence of potential (Lyaponuv function) in limit cycle (65). We will explicitly show the existence of evolutionary potential in a limit cycle and demonstrate its generic implication. It is an illustration on the connection between the proposed laws discussed in section III and the classical formulations in section IV. The example also serves an indication for the practical difficulty in the construction of the evolutionary potential out of the classical formulations.

A. Limit Cycle in Physics

The goal of this subsection is twofold: to provide a concrete anchoring point where all the quantities are physically conceivable and to obtain an explicit example of potential with expected properties in the presence of limit cycle.

In physics, the general dynamical equation for a *massless* particle in two dimensional state space may be expressed, with both deterministic and stochastic forces (30):

$$[A(\mathbf{q}) + T(\mathbf{q})]\dot{\mathbf{q}} = \nabla\psi(\mathbf{q}) + \xi(\mathbf{q}, t) ,$$

identical to Eq.(1), and supplemented by the relationship on the stochastic force:

$$\langle \xi(\mathbf{q}, t)\xi^\tau(\mathbf{q}, t')\rangle = 2A(\mathbf{q})\,\epsilon\,\delta(t - t') ,$$

and $\langle \xi(\mathbf{q}, t)\rangle = 0$, identical to Eq.(2). Here $\mathbf{q}^\tau = (q_1, q_2)$ with q_1, q_2 the two Cartesian coordinates of the state space, which may be perceived as the position space of the massless particle. The transpose is denoted by the superscript τ, and $\dot{\mathbf{q}} = d\mathbf{q}/dt$.

The scalar function ψ corresponds to the usual potential energy function. Its graphical representation in the state space is a landscape. The antisymmetric matrix T represents the dynamics which conserves the potential, corresponding to the Lorentz force in physics, determined by the magnetic field. The matrix A represents the dynamics which increases the potential (Please note that the evolutionary potential has an opposite sign as that in physics.), the dissipation in physics. This matrix may be called the friction matrix as used in physics. The simplest realization of the friction matrix is a constant matrix

$$A = \eta \begin{pmatrix} 1 & 0 \\ 0 & 1 \end{pmatrix} \tag{56}$$

with the friction coefficient η. The simplest realization of the antisymmetric matrix is

$$T = b \begin{pmatrix} 0 & -1 \\ 1 & 0 \end{pmatrix} \tag{57}$$

with b as the strength of magnetic field. With such a realization of those matrices, Eq.(1) becomes

$$\eta \dot{\mathbf{q}} + b\hat{z} \times \dot{\mathbf{q}} = \nabla \psi(\mathbf{q}) + \xi(\mathbf{q}, t) , \tag{58}$$

the very familiar form of equation of motion for a massless particle in the presence of frictional and Lorentz forces. Here $\hat{z}$ is the unit vector perpendicular to the state space formed a plane by q_1 and q_2, indicating the direction of the magnetic field b with the electric charge taken to be 1. The word "massless" here implies that the mass of the particle is so small it can be taken to zero in the present dynamical consideration, and the particle dynamics is dominated by the frictional and Lorentz forces.

The friction matrix A is connected to the stochastic force ξ by Eq.(2), which guarantees that it is semi-positive definite and symmetric. All T, A, ψ can be nonlinear functions of the state variable $\mathbf{q}$ as well as the time t. The numerical parameter ϵ corresponds to an effective temperature, which can be taken to be zero to recover the deterministic dynamics. It has been shown in section IV that if a steady state distribution $\rho(\mathbf{q})$ in state space exists,

$$\rho(\mathbf{q}) = \frac{1}{Z} \exp \left(\frac{\psi(\mathbf{q})}{\epsilon} \right) ,$$

a Boltzmann-Gibbs type distribution function (4), same as Eq.(6). Here Z is the partition function $Z = \int d\mathbf{q} \, \exp(\psi(\mathbf{q})/\epsilon)$. The only use of "mass" is to establish such a classical equilibrium distribution physics, as illustrated by Eq.(38). Above equation implies that for dynamics which repeats itself indefinitely, such as limit cycle, the potential should be the same along such trajectory.

It should be pointed that the potential function $\psi(\mathbf{q})$ exists from the beginning by construction. This is one of most useful and important quantitative concepts in physics. If the stochastic force could be set to be zero, $\xi(\mathbf{q}, t) = 0$, that is, the deterministic dynamics, the dynamics of this massless particle always decreases its potential energy:

$$\begin{aligned} \dot{\mathbf{q}}^\tau \nabla \psi(\mathbf{q}) &= \dot{\mathbf{q}}^\tau [A(\mathbf{q}) + T(\mathbf{q})] \dot{\mathbf{q}} \\ &= \dot{\mathbf{q}}^\tau A(\mathbf{q}) \dot{\mathbf{q}} \\ &\geq 0 . \end{aligned}$$

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Here $\dot{\mathbf{q}}^\tau \nabla\psi(\mathbf{q}) = \dot{\mathbf{q}} \cdot \nabla\psi(\mathbf{q})$. The zero occurs only at the invariant sets: fixed points (point attractors), limit cycles (periodic attractors) and/or more complicated ones. Hence the potential function has the usual meaning of Lyapunov function. We already encountered this property in the discussion of the first law.

To explicitly model a limit cycle, we choose following forms for the friction matrix A, the anti-symmetric matrix T, and the potential ψ, assuming the limit cycle occurs at $q_{limit\ cycle} = 1$ ($q = \sqrt{q_1^2 + q_2^2}$):

$$A = \frac{(q^2 - 1)^2}{(q^2 - 1)^2 + 1} \begin{pmatrix} 1 & 0 \\ 0 & 1 \end{pmatrix} , \tag{59}$$

$$T = (q - 1)\frac{q^2}{(q^2 - 1)^2 + 1} \begin{pmatrix} 0 & -1 \\ 1 & 0 \end{pmatrix} , \tag{60}$$

$$\psi = -\frac{1}{2}(q - 1)^2 . \tag{61}$$

The potential ψ given in Eq.(61) is rotational symmetric in the state space and $|\nabla\psi| = |q-1|$. It has a local minimum $\psi = -1/2$ at $q = 0$, which is a cusp, and the maximum $\psi = 0$ at $q = 1$, which is a cycle in the state space. Hence the potential takes the shape of a Mexican hat.

If the friction matrix A would be zero, the dynamical trajectory of the massless particle would move along the equal potential contour determined by the initial condition, which would be a cycle according to above chosen potential. In the presence of nonzero friction matrix, this is not true. What will be our concern is the behavior near the minimum of the potential function: When q is sufficiently close to 1, does the particle trajectory asymptotically approach the cycle of $q = 1$ and eventually coincide with it? If the answer is positive, we have a limit cycle dynamics. We will demonstrate below that it is indeed possible.

For a deterministic dynamics, we can set $\epsilon = 0$ in Eq.(1) and (2): setting the stochastic force to be zero. The dynamical equation can then be rewritten as

$$\dot{\mathbf{q}} = [A(\mathbf{q}) + T(\mathbf{q})]^{-1} \nabla\psi(\mathbf{q}) . \tag{62}$$

With the choice of Eqs. (59,60), we have

$$[A + T]^{-1} = \frac{1}{\det(A + T)} \left[\frac{(q^2 - 1)^2}{(q^2 - 1)^2 + 1} \begin{pmatrix} 1 & 0 \\ 0 & 1 \end{pmatrix} \right.$$

$$-(q-1)\frac{q^2}{(q^2-1)^2+1})\begin{pmatrix} 0 & -1 \\ 1 & 0 \end{pmatrix}\Bigg] \tag{63}$$

and

$$\det(A+T) = \left[\frac{(q^2-1)^2}{(q^2-1)^2+1}\right]^2 + \left[\frac{(q-1)q^2}{(q^2-1)^2+1}\right]^2 . \tag{64}$$

Near $q=1$, we have

$$[A+T]^{-1} = \frac{1}{q-1}\Bigg[-(1-2(q-1))\begin{pmatrix} 0 & -1 \\ 1 & 0 \end{pmatrix}$$
$$+4(q-1)\begin{pmatrix} 1 & 0 \\ 0 & 1 \end{pmatrix} + O((q-1)^2)\Bigg] . \tag{65}$$

In terms of radial coordinate q and azimuthal angle θ in the polar coordinate representation of the state space, using the small parameter expansion given in Eq.(65) and following Eq.(62) we have, to the order of $q-1$,

$$\dot{q} = -4(q-1) , \tag{66}$$
$$\dot{\theta} = 1 - 2\frac{q-1}{q} . \tag{67}$$

The solution is

$$q(t) = 1 + \delta q_0 \exp\{-4t\} , \tag{68}$$
$$\theta(t) = \theta_0 + t + \frac{1}{4}\ln\frac{1+\delta q_0\exp\{-4t\}}{1+\delta q_0}$$
$$+\frac{1}{2}\ln(1+\delta q_0\exp\{-4t\}) . \tag{69}$$

Here δq_0 ($|\delta q_0| << 1$) is the starting radial position of the particle measured from $q=1$ and θ_0 its the starting azimuth angle. Indeed, the solution demonstrates the asymptotical approaching to the cycle $q=1$, and the motion never stops. Unstable and metastable limit cycles may be constructed in the similar manner.

Though above construction does show that based on the physics knowledge one can construct limit cycle with the potential, the example of Eqs.(59-61) appears contrived. We should, however, point out that there are several generic features in our construction.

(i) To have an indefinite motion on a closed trajectory, because of energy conservation, the friction, or better the friction matrix here, must be zero.

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(ii) Because of the asymptotic motion is on the equal potential contour, a Lorentz force type must exist to keep the motion on the contour. This means that the antisymmetric matrix should be finite along the equal motion contour when the potential gradient is finite. The speed of the *massless* particle moving along the contour will be determined by the ratio of the strength of the Lorentz like force to that of the gradient of the potential.

(iii) The limit cycle should be robust: Small parameter changes should only have a small effect on the limit cycle, the (stable) limit cycle should be at the minimum of the potential. As a consequence, the potential gradient at the maximum is zero, which would imply that the friction matrix must go to zero faster than that of the potential gradient when approaching to the maximum to avoid the potential taking singular values. This means that at the limit cycle the dynamics is conservative.

(iv) Furthermore, to ensure the massless particle moves in the same direction on both sides of the limit cycle, the magnetic field should change its sign at the limit cycle. All those features are explicitly implemented in the choice, Eqs.(59-61).

Three additional remarks are in order.

(v) For simplicity of calculation we have chosen the friction matrix to be proportional to aunit matrix in Eq.(59). One can check that any positive definite symmetric matrix can lead to same conclusion, as long as its strength goes to zero in a higher order comparing to that of the potential gradient.

(vi) Although the friction matrix A is zero when approaching to the limit cycle, $[A + T]^{-1} + [A - T]^{-1}$ is not, to which we will come back in subsection V.C when discussing the diffusion matrix D.

(vii) It should be emphasized here that the potential has a dual role: Its gradient is the driving force in dynamics, expressed in Eq.(1) or Eq.(62), and it determines the final steady state distribution, expressed in Eq.(6).

We should point out that the Mexican hat type potential has been suggested for limit cycle previously (64). However, to our knowledge there is no prior discussion of the associated magnetic and dissipative forces similar to the present and next subsections.

B. Limit Cycle in Classical Formulation

In the above subsection we have shown that starting with potential one can construct limit cycle. In this subsection we will show the reverse. One may regard that the demonstration of the co-existence of limit cycle with the potential in above subsection may be special: The massless particle moves along the potential minimum with both zero friction and zero transverse matrices, a rather nice but contrived picture from physics. One may wonder that whether or not in a typical limit cycle in dynamical systems a potential can be constructed. We will demonstrate in this subsection that the answer to such question is positive.

It has been suggested that a simple limit cycle in two dimensions would take following form for its dynamical equation in a polar coordinate representation (58):

$$\dot{q} = R(q) , \tag{70}$$

$$\dot{\theta} = \Phi(q) . \tag{71}$$

Here the smooth functions R, Φ have properties $R(q = 1) = 0$ is a fixed point in the radial coordinate and $\Phi(q = 1) = constant$. We point out that mathematically any shape of limit cycle in two dimension can be deformed into a cycle and that near this limit cycle the dynamical equation can be mapped onto above form by a nonlinear coordinate transformation. Hence Eq.(70) and (71) may be regarded as a representation for a generic limit cycle in two dimension.

The comparison between Eqs.(66,67) and Eqs.(70,71) immediately suggests what considered in section II is just such a typical limit cycle. The construction of potential from Eq.(70) and (71) is also immediately suggested: Given functions $R(q)$ and $\Phi(q)$, there exist the friction matrix S, the potential ψ, and the antisymmetric matrix T. In fact, we have three independent quantities to be constructed instead of two. Such uniqueness question has been addressed in section IV.

To construct the potential from Eq.(70) and (71), we go back to Eq.(62). Using $[A + T]^{-1} = G = D + Q$ defined in Eq.(28), Eq.(2) may be rewritten as

$$\dot{\mathbf{q}} = [D(\mathbf{q}) + Q(\mathbf{q})]\nabla\psi(\mathbf{q}) . \tag{72}$$

Here again D is a symmetric and positive definite matrix and Q an antisymmetric matrix.

For simplicity, we choose D to be the identify matrix,

$$D = \begin{pmatrix} 1 & 0 \\ 0 & 1 \end{pmatrix} , \tag{73}$$

and choose

$$Q = a(q) \begin{pmatrix} 0 & -1 \\ 1 & 0 \end{pmatrix} . \tag{74}$$

Here $a(q)$ is a scalar function of q.

In accordance with the rotational symmetry in Eq.(70) and (71), we also choose the potential function depending only on the radial coordinate q, $\psi(q)$. With above choices, in the polar coordinates Eq.(72) implies

$$\dot{q} = \frac{d\psi(q)}{dq} , \tag{75}$$

$$q\dot{\theta} = a(q)\frac{d\psi(q)}{dq} . \tag{76}$$

Comparing above two equations with Eq.(70) and (71) we have

$$\frac{d\psi(q)}{dq} = R(q) , \tag{77}$$

$$b(q) = q\frac{\Psi(q)}{R(q)} . \tag{78}$$

Thus,

$$\begin{aligned} A(q) + T(q) &= [D(q) + Q(q)]^{-1} \\ &= \begin{pmatrix} 1 & q\frac{\Psi(q)}{R(q)} \\ -q\frac{\Psi(q)}{R(q)} & 1 \end{pmatrix}^{-1} \\ &= \frac{1}{1 + \left(q\frac{\Psi(q)}{R(q)}\right)^2} \begin{pmatrix} 1 & -q\frac{\Psi(q)}{R(q)} \\ q\frac{\Psi(q)}{R(q)} & 1 \end{pmatrix} . \end{aligned} \tag{79}$$

This gives,

$$A(q) = \frac{1}{1 + \left(q\frac{\Psi(q)}{R(q)}\right)^2} \begin{pmatrix} 1 & 0 \\ 0 & 1 \end{pmatrix} , \tag{80}$$

$$T(q) = \frac{1}{1 + \left(q\frac{\Psi(q)}{R(q)}\right)^2} q\frac{\Psi(q)}{R(q)} \begin{pmatrix} 0 & -1 \\ 1 & 0 \end{pmatrix} . \tag{81}$$

Eqs.(77,80,81) are one explicit construction of potential for the limit cycle dynamics described by Eq.(70) and (71), corresponding to the dynamics described by Eq.(1) and (2).

When approaching to the limit cycle, $q \to 1$, $R(q) = O(q-1)$ and $\Phi(q) = O(1)$, and,

$$\frac{d\psi(q)}{dq} = O(q-1) , \tag{82}$$

$$T(q) = O(q-1) \begin{pmatrix} 0 & -1 \\ 1 & 0 \end{pmatrix} , \tag{83}$$

$$A(q) = O((q-1)^2) \begin{pmatrix} 1 & 0 \\ 0 & 1 \end{pmatrix} . \tag{84}$$

This has the same structures as those in Eqs.(59-61). The friction matrix A indeed vanishes faster, though the diffusion matrix D here always remains a constant. The dynamics eventually becomes non-dissipative along the limit cycle from the point of view of Eq.(1). This completes the discussion of construction of potential for a limit cycle in two dimension.

For an arbitrary limit cycle, the construction of potential from the classical formulation will start from Eq.(24) and (27), which are first order partial differential equations. The behavior near a limit cycle should resemble that described by Eqs.(82-84). Such behavior provides the necessary boundary condition to solve Eq.(24) and (27). Only in some extremal cases the solving of partial differential equations can be turned into the solving of algebraic equation, as showed in this subsection.

Nevertheless, we should point out an interesting feature. On one side it is known from the theory of dynamical systems that a limit cycle is robust (35). Any small parameter change in the equation would not lead to its disappearing. On the other side, from the demonstration in section II which is based on the understanding from physics, the existence of the limit cycle is a result of a very delicate balance between all dynamical elements: The friction matrix, the gradient of potential function, and the antisymmetric matrix. They are all zero at the limit cycle, and when approaching to the limit cycle, the friction matrix vanishes faster. How this paradoxical feature would play a role in our better understanding limit cycle and its control will be an interesting problem for further exploration.

C. Diffusion *vs* Ascendency (Friction)

There are two mathematical subtleties. First, it is known that even with a limit cycle the dynamics is dissipative, reflecting by the fact that in general $\nabla \cdot \mathbf{f} \neq 0$, where $\mathbf{f}$ is defined by Eq.(14). This is also expressed by the fact that the so-called diffusion matrix, D defined in Eq.(15), is finite even at the limit cycle. Because it is dissipative, it would be difficult to conceive a constant potential (or a Lyapunov function) along the limit cycle on which the dynamics repeats itself indefinitely. The delicate point is that, as shown in our above demonstration, that the friction matrix A is zero along the limit cycle does not implies the diffusion matrix D is zero. In fact, it is finite according to Eq.(22) and (27):

$$
\begin{aligned}
D &= \frac{1}{2}[G + G^\tau] \\
&= \frac{1}{2}[(A + T)^{-1} + (A - T)^{-1}] \, .
\end{aligned} \tag{85}
$$

An explicit verification can be obtained from Eq.(65): $D = 4$ while $A = 0$ along the limit cycle. An important and direct implication of present construction is that the statement, that there is no evolutionary potential (or Lyapunov function) in limit cycle in (65), is not valid.

We come to the second subtlety. For completely deterministic dynamics Lyapunov function cannot be uniquely defined: If one finds one Lyaponov function, one finds many. This is illustrated by the present construction that additional information from the noise is needed to make the construction unique: different diffusion matrix would lead to different potential function. We already encountered this issue when construction potential from Eq.(70) and (71), without the specification of noise. However, this freedom may provide a method to select the best suitable Lyapunov function or potential function to one's problem by choosing appropriate form of the diffusion matrix.

It is worthwhile to point out a simple mathematical fact that the typical gradient systems in dynamical systems theory corresponds to the zero transverse matrix, $T = 0$, in the present construction. It is the case when the detailed balance condition is satisfied. No limit cycle is possible in this case. In dynamics described by gradient systems the trajectory could follow the most rapid descendant path along the landscape defined by the potential. In this case it is easy to identify the potential as the landscape function. For a general dynamics where the transverse matrix is not zero, the trajectory would not follow the most rapid descendant

route along the potential, as expressed by Eq.(1) or Eq.(62). Nevertheless, the meaning of the potential remains the same as that in gradient systems: driving the dynamics and determining the final steady state distribution.

VI. F-THEOREM: FURTHER EXPLORATIONS

It is now clear that the Fisher's original formulation of the fundamental theorem of natural selection is in the domain of classical formulation. To illustrate this point, let us consider the situation that the detailed balance condition, Eq.(48), is satisfied. From Eq.(14) and (15), we have

$$\dot{\mathbf{q}} = D(\mathbf{q})\nabla\psi(\mathbf{q}) + \zeta(\mathbf{q}, t) . \tag{86}$$

Thus, the rate of increase is indeed proportional to the variance D. This result can be made most explicit in one dimension. In one dimension, the transverse matrix is zero by definition. Near a potential peak, taking it as $q_{peak} = 0$,

$$\psi(q) = \psi(0) - \frac{1}{2}Uq^2 + O(q^3) , \tag{87}$$

and

$$\nabla\psi = -Uq . \tag{88}$$

Here in one dimension U is a positive constant. If we also drop the noise term for simplicity, from Eq.(86) and (87) we have

$$\begin{aligned}
\frac{\frac{d(\psi(q)-\psi(0))}{dt}}{|\psi(q) - \psi(0)|} &= -2\frac{\dot{q}}{q} \\
&= 2D(0)U .
\end{aligned} \tag{89}$$

The rate of increase in evolutionary potential is indeed proportional to the variance D in the classical formulation, with a suitable choice of unit as indicated by the positive constant U. This corresponds precisely to Fisher's original statement.

It is interesting to note that under those conditions the rate of increase in evolutionary potential is proportional to the inverse of the variance A ($D = 1/A$ under detailed balance condition) in the present formulation, Eq.(2). There is nevertheless no contradiction here. In the present formulation the meaning is taken from the fluctuation-dissipation theorem: the return to the evolutionary potential peak and the fluctuation from the peak are governed by

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the same process. This meaning is also implied in Fisher's fundamental theorem of natural selection. No other direct connection between rate of increase in evolutionary potential and the variance A has been stated in the present formulation, except what can be obtained from Eq.(1) and (2).

Such demonstration suggests that Fisher's original formulation is only exact near the peak of evolutionary potential and under the condition of detailed balance. While the requirement to be at the vicinity of the peak does not appear to a major barrier to generalize Fisher's original statement to nonlinear case of far from the peak, the requirement of detailed balance is too strong. The latter can be violated even near the peak, if transverse matrix T is no longer zero. It causes the breakdown of detailed balance. In the absence of detailed balance condition, we no longer have the simple relation $D = 1/A$, as implied by Eq.(21). It is known that the breakdown of detailed balance is common in population genetics. This would result in the situation that the variance, the diffusion constant D, can only partially determine the rate of increase in evolutionary potential. We further illustrate this point below.

Near a potential peak, taken to be $\mathbf{q}_{peak} = 0$, in dimension higher than one, we may approximate the diffusion matrix D by a constant matrix. The force $\mathbf{f}$ can be linearized:

$$\mathbf{f}(\mathbf{q}) = S\mathbf{q} . \tag{90}$$

Here S is the selection matrix defined by Eq.(18) in subsection IV.A and is a constant matrix in the linear case. Similarly, the Wright evolutionary potential can be expressed by a constant potential matrix U:

$$\psi(\mathbf{q}) = \psi(0) - \frac{1}{2}\mathbf{q}^\tau U\mathbf{q} , \tag{91}$$

and the ascendant matrix A is also a constant matrix. Here U, A, D are symmetric and positive definite while S is asymmetric.

Given D and S in the classical formulations, U, A and T can be uniquely determined (44). In general they are complicated function of D and S. Formally, we still have a simple formula similar to Eq.(89):

$$\frac{\frac{d(\psi(q)-\psi(0))}{dt}}{|\psi(q) - \psi(0)|} = 2\frac{\mathbf{q}^\tau U(D,S)DU(D,S)\mathbf{q}}{\mathbf{q}^\tau U(D,S)\mathbf{q}} . \tag{92}$$

There is, however, no simple interpretation of this formula in the absence of detailed balance condition. In the limit there is a strong asymmetric dynamics, that is, if the transverse

matrix T is much larger than the ascendant matrix A: $|\det(T)| >> \det(A)$, to the first order in ascendant matrix we have

$$\frac{\frac{d(\psi(q)-\psi(0))}{dt}}{|\psi(q)-\psi(0)|} = 2\frac{(T^{-1}U\mathbf{q})^{\tau}A(T^{-1}U\mathbf{q})}{\mathbf{q}^{\tau}U\mathbf{q}}\;, \tag{93}$$

which is proportional to the variance A in the present formulation, because A, T, U are independent quantities. Again, there is no contradiction here: it is still that the return to the evolutionary potential peak and the fluctuation from the peak are governed by the same process.

Initially there may be a large deviation from the peak and the fluctuation may be relative small. As time progresses, the system gets closer and closer to the peak, and the deviation $|\psi(0)-\psi(\mathbf{q})|$ becomes smaller and smaller. Eventually we can no longer differentiate the deviation from the fluctuation. Both the return to the peak and the fluctuation have to be considered simultaneously. Statistically, the distribution of state variable averaged over time is then given by the distribution in the form of Eq.(8), well-known in population genetics (42). This suggests that the staying in the peak is a dynamical process: the balance of fluctuation from the peak and the tendency to return. This is similar to van Valen's Red Queen hypothesis (78): in order to stay at the same position the motion is required.

The partial increase in evolutionary potential by variance has already been observed in population genetics (23). In section V we have discussed an extreme case: while the variance D in the classical formulation is finite, there is no change at all in the evolutionary potential when the system moves along a limit cycle. Such a consideration suggests that Fisher's original formulation of the fundamental theorem of natural selection is indeed not general enough. The present formulation can deal with those situations in a consistent manner. Above analysis also suggests that the conservative dynamics represented by the transverse matrix T must be an integral part of general evolutionary dynamics.

We have now demonstrated that the contexts of the fundamental theorem of natural selection and the fluctuation-dissipation theorem are the same: the connection between the fluctuation and the ability to search for peaks. Nevertheless, there is still an imperfection in those formulations: A potential peak, or, in general the evolutionary potential, is implicitly assumed in their statements. On the other hand, in the present formulation of the F-Theorem there is no reference to the evolutionary potential. The connection between the fluctuation and the ability to search in state space is still kept. This suggests that the F-Theorem is

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a generalization of the fundamental theorem of natural selection, making it applicable to the cases where there is no change in evolutionary potential, such as the case of limit cycle dynamics in section V or the case of speciation in the holey adaptive landscape (28).

VII. DISCUSSIONS

Before further discussion of the implications of the present mathematical formulation, it should be kept in mind that the three laws must be regarded as a first attempt to formulate mathematically what the evolutionary dynamics might be. Further generalizations or extensions are needed. For example, Gaussian-white noise assumption may well be the first step towards a complete modelling of stochasticity in evolution. We have not discussed the nonwhite noises, though we believe the presentation formulate gives us a good starting point to do so. In this connection we point out that the famous $1/f$ noise ($s = 0$ as formulated in Ref.[(46)]) may be constructed from white noise ($s = 1$ as formulated in Ref.[(46)]) (6). The present discussion has been confined to stochastic differential equations and related Fokker-Planck equations. We believe generalization to stochastic partial differential equations may be needed for a complete discussion of speciation. In addition, in the present review the focus is dynamics, not the structure of each dynamical element. Those dynamics elements may take different forms at different levels of description, an important subject completely outside the present scope.

Having made those qualifying observations, we nevertheless remark that although the proposed three laws for evolutionary dynamics are based on the continuous representation in terms of time and population, it is possible that main features discussed in the present review should survive in more general cases: the ultimate selection by Wright evolutionary potential, the adaptive nature of ascendant matrix, the conservative dynamics represented by the antisymmetric matrix, and the presence of stochastic drive. We have emphasized the intrinsic stochastic nature of evolutionary process, not those due to imperfections from measurement and/or observation.

A. Consistency and Compactness

In the present attempt to unify approaches from biological and physical sciences, the possible existence of general laws such as expressed by Eq.(1) and (2) in a compact and consistent manner should not be too surprising. One has to consider two important principles which have been rigorously validated:

(i) Simple equations can generate extremely complicated patterns and phenomena (35; 51; 58);

(ii) Each level of description has its own laws which cannot be derived in a naive reductionist manner (2; 10; 29). The connections between levels are asymptotic and emerging phenomena frequently occur at higher levels.

There are several quantitative advantages in the present formulation of evolutionary theory. With the Wright evolutionary potential defined as in Eq.(1), an independent way for its calculation has been obtained. It adds more predictive power to the evolutionary dynamics.

As expressed by Eq.(2) and discussed in section 2.4, Fisher's fundamental theorem of natural selection (the F-Theorem) becomes transparent and indispensable in the present formulation of evolutionary dynamics. This may provide a much-needed step to better understand Fisher's great insight.

Combining both Fisher's and Wright's insights, the Wright evolutionary potential and the F-Theorem provide a quantitative measure to discuss robustness, stability, and the speciation. Eq.(9) is such an example: both variance and the evolutionary potential are needed to obtain the formula. What has been new in the present article is the glue to put both Fishers and Wrights insights together: Evolutionary dynamics has a conserved part in which the Wright evolutionary dynamics would not change. This conservative part of dynamics is represented by the transverse matrix in the present article, and appears to have been overlooked in literature.

It is interesting to point out the remarkable similarity between the adaptive landscape of Wright (83) and the developmental landscape of Waddington (79). In fact, there is a remarkable similarity between the adaptive speciation (18) and development biology (79): Their landscapes are identical. The present mathematical formulation should be able to deal with both cases. An example of the gene regulatory network in phage λ has already been studied successfully by Zhu *et al.* (85; 86). This suggests a unification between genetics and

developmental biology.

B. Usefulness

However, one may wonder about the need to use Eq.(1) and (2) instead of the classical formulation of Eq.(14) and (15) or Eq.(39): After all their equivalence has been demonstrated above. Here we offer three reasons that Eq.(1) and (2) can be useful:

(i) Quantities presented in Eq.(1) can be directly related to experimental observation. For example, Eq.(6) gives a direct connection between the Wright evolutionary potential and the population density in steady state. By observing the dynamical behaviors, information on the ascendant and transverse matrices can be obtained. Also, Eq.(9) can relate stability to the Wright evolutionary potential. This direct contact with experimental data is an indication of the autonomy of the focused level of description.

(ii) Eq.(14) and (39) lack the visualizing ability for the global dynamics behavior. For example, in a nonlinear dynamics with multiple local maxima, it is not clear from Eq.(14) and (15) which maximum is the highest and how easy it might be to move from one maximum to another. One could find this answer by a direct real time calculation. But this is usually computationally demanding, if not impossible. For deterministic dynamics it is impossible. Instead, the Wright evolutionary potential gives a quantitative and visualizable answer to such inquiry.

(iii) Eq.(1) and (2) give an alternative modelling of evolutionary dynamics, which can be advantageous in certain situations. For example, the direct use of evolutionary potential (fitness function by Stewart) in Stewart's modelling (72) makes the symmetry-breaking idea in speciation very transparent from statistical physics' point of view.

C. Biology and Physics

Finally, we point out an interesting mutual reduction loop between biology and physics. The present formulation suggests that the laws as expressed by Eq.(1) and (2) are stochastic and dissipative. They represent the generic features of the dynamics in biology. For example, the mathematical structure used in the present review was first suggested in our study of the outstanding robustness puzzle in a genetic switch (85; 86), after a long search

for a way to quantify robustness and stability. On the other hand, the dynamical law of physics is deterministic and conservative, as manifested in the classical Newtonian dynamics. In the discussion of the first law of Darwinian dynamics we remarked that one may regard the Newtonian dynamics as a special case of the first law when the nonconservative force represented by the ascendant matrix is zero. Since the first law is a special case of the second law, the Newtonian conservative dynamics may be further regarded as a special case of the present second law, hence a special case of the Darwinian dynamics. The opposite statement also exists: Under an appropriate condition of treating the dissipative dynamics as a subdynamics, a typical approach to model open systems in physics, equations in the form of Eq.(1) and (2) can be derived from the Newtonian dynamics (5; 7; 22; 27; 46). Therefore, the Darwinian dynamics may also be regarded as a special case of the Newtonian dynamics.

Darwinian dynamics places an emphasis on the statistics while the Newtonian dynamics on the determinism. Which one would be more appropriate and fundamental to describe Nature is both a philosophical and a serious scientific research topic. The approach from the dissipative dynamics side can be found the work of Prigogine school (59) and the approach from the conservative dynamics side can be found, for example, in Ref.[(22)] and [(27)]. It appears suitable to end this subsection with a quotation from Einstein who had thought deeply into this issue (21):

"Concerning the question of Statistics against Determinism, this is the way it appears: From the point of view of immediate experience there is no such thing as exact determinism. Here there is no disagreement. The question is whether or not the theoretical description of nature must be deterministic. Beyond that, the question is whether or not there exists generally a conceptual image of reality (for isolated case), an image which is in principle completely except from statistics. Only on this subject do opinions differ."

VIII.   FURTHER NOTES ON LITERATURE

While it is impossible to review all theoretical literature on Darwinian dynamics in the present article, in this section we discuss a few selected works related to the present formulation. We hope that it may be helpful to readers for further pursuing the subject.

One of most extensive discussions on Darwinian evolutionary dynamics from biological

point of view is provided by Gould (32). He held a view against a more quantitative formulation, calling it the hardening of Darwinian theory. In particular, the first three exceptions of Fisher's fundamental theorem of natural selection were summarized in his book as the exceptions of contingency, individuality, and interaction. Those exceptions, according to Gould, simply excluded Fisher's fundamental theorem of natural selection from biology. In the light of present formulation, while Gould's critiques of Fisher is correct, it is nevertheless based on wrong formulation and improper analogy. For example, as discussed in subsection IV.D, the fitness should not be interpreted as the entropy in physics, and the proper analogy of Fisher's fundamental theorem of natural selection should be the fluctuation-dissipation theorem in physics, formulated as the F-Theorem in the present article. With such re-interpretation, the Gould's critique disappears, because all Fisher's five exceptions disappear. Nevertheless, Gould's book still serves as one of the best biological sources to understand evolution.

On a conceptual level, the controversies and key concepts of Darwinian evolutionary theory have been concisely summarized by a recent book by Mayr (54). It is a must read book. His summary of Darwinian dynamics that "the basic Darwinian formula - evolution is a result of genetic variation and its ordering through elimination and selection - is sufficiently comprehensive cope with all natural eventualities" is indeed a most proper verbal presentation of the present second law at genetic level. It is, however, puzzling to note that, whether accidental or intensional, there is a de-emphasis on the quantitative aspects of population genetics in Mayr's book. It is hard to conceive the presentation of the modern synthesis of Darwinian theory without a detailed discussion on Wright and Fisher, particularly on the fundamental theorem of natural selection.

In addition to the summary of mathematical results since Fisher and Wright on population genetics by Ewens (23), the formulation of Darwinian dynamics in the line of classical formations has been presented in detail by Michod (55). Both the Wright's evolutionary landscape and Fisher's fundamental theorem of natural selection occupy an prominent place in the book. Some 28 different usages of the term *fitness* are compiled in his Appendix B, which may be regarded as a support to use the term Wright evolutionary potential in the present review, instead of the loaded term *fitness*. Also interesting is his emphasis on the cooperation and interaction, which may shed a light on the controversy regarding to the Wright's shift balance theory and related speciation problem (31; 63).

The discussion by Turchin (74) on debate of the existence of general laws in biology

should be interesting. Concrete examples in ecological dynamics have been discussed in detail in his book. Nevertheless, it seems that Turchin has not emphasized the role played by stochasticity in general laws, though he does emphasize the need to use statistics in data analysis. Much of his detailed discussions is deterministic in nature and hence may be viewed as the unfolding of the first law discussed in the present article. For example, his first principle of exponential growth (decrease) may be regarded as a special case of the stable fixed point at infinity (zero). A discussion of ecological dynamics from the adaptive landscape perspective can be found in Schluter's book (68).

One of the best discussions on the classical formulation of evolutionary dynamics in a general setting is certainly by Nicolis and Prigogine (59). A parallel and stimulating approach can be found in the exposition of synergetics (36). One of the best discussions on the fluctuation-dissipation theorem in physics can be found in Ref.[(84)]. We should also mention that the concept of evolutionary potential has been elegantly employed by Stewart (72) in his discussion of speciation and by many other researchers (18) in the deterministic study of adaptive speciation.

IX. CONCLUSIONS

We have postulated three laws to mathematically describe the evolutionary dynamics: the law of Aristotle, the law of Darwin, and the law of Hierarchy. The first law, the law of Atistotle, emphasizes the deterministic aspect of the evolutionary dynamics. This law defines the reference point for discussion. The most fundamental equation, the second law or the law of Darwin, has been expressed in a unique form of stochastic differential equation. Four dynamical elements have been introduced into the present formulation: the ascendant matrix, the transverse matrix, the Wright evolutionary potential, and the stochastic drive. The final and ultimate selection is represented by the Wright evolutionary potential which determines the steady state distribution. At any given time, the instant selection is determined by all four dynamical elements encoded in the second law, which would not necessarily increase the Wright evolutionary potential. Both the tendencies for adaptation and for optimization are encoded in the F-Theorem. The hierarchical nature of biological description is encoded in the third law whose precise mathematical procedure depends the specific problem in consideration. This is illustrated by the existence of several

integrations of stochastic differential equations. Table I gives a summary of the present formulation.

We have also demonstrated that present three laws are consistent with classical approaches in evolutionary biology, but appear more suitable to discuss stability and other phenomena quantitatively. Various important results, such as Fisher's fundamental theorem of natural selection and Wright's adaptive landscape, as well as the developmental landscape, are unified in the present formulation in a natural manner. The inconsistent understandings of those two central concepts of Fisher and Wright, raised either from the original vague verbal statements or from intrinsical mathematical difficulties, have been discussed and clarified. The main goal of the present formulation is to resolve the outstanding and historical problems rather than to complicate life. Indeed, it appears to form a consistent and quantitative foundation for further discussion of the Darwinian dynamics.

Table I: Laws of Darwinian dynamics and the F-Theorem

The central dynamical equation is the Second Law supplemented by the F-Theorem.

ψ: Wright evolutionary potential, ultimate selection

T: antisymmetric transverse matrix, conservative dynamics

A: ascendant matrix, adaptive dynamics

ξ: stochastic drive, random

$\mathbf{q}$: state variable vector

	mathematical expressions	alternative names	comments
First Law	$\{\mathbf{q}\} \rightarrow \{\mathbf{q}_{attractor}\}$	law of Aristotle	determinism
Second Law	$[A(\mathbf{q}) + T(\mathbf{q})]\dot{\mathbf{q}} = \nabla\psi(\mathbf{q}) + \xi(\mathbf{q},t)$	law of Darwin	stochastic dynamics
F-Theorem	$\langle \xi(\mathbf{q},t)\xi^{\tau}(\mathbf{q},t')\rangle = 2A(\mathbf{q})\,\delta(t-t')$	Fisher's FTNS	adaptation and optimization
Third Law	$m \rightarrow 0$	law of hierarchy	multiple time scales

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[88] If the reader has followed this far, it may be justifiable to read a few explanationary words and informal comments.

1). An earlier eprint available as q-bio/0403020. The current version is more than twice of length as that of the earlier one, though no change in the core structure. This is a result of my effort to apply a powerful biological idea (re)emerged from our phage lambda genetic switch to the most fundamental issues in biology: the evolution. At the time of posting the earlier version, none of our work related to phage lambda were published. The current version was published in **Physics of Life Reviews**, Volume **2**, Issue 2, June **2005**, Pages **117-156**; http://www.sciencedirect.com/science/journal/15710645; doi:10.1016/j.plrev.2005.03.002.

2). The reader may not surprised to learn that the present manuscript has been regarded as provocative by a fraction of experts. In fact, it was rejected by a decent biological journal because the editor viewed it too provocative to be publishable, withouth going through the reviewing process.

3). Nevertheless, I believe, if my understanding of evolution is correct, that Darwinian dynamics is univeral. Based on this consideration I have applied the present formulation to solve a specific open problem posted in Artifical Life as one of grand challenges. I submitted my manuscript to Artifical Life. It did get reviewed, but rejected. My manuscript was then posted

as http://xxx.lanl.gov/PS_cache/nlin/pdf/0406/0406002.pdf. One may check the recent issues in Artifical Life and will find that the Darwinian dynamics does apply to it, too. Here I list the name of Artifical Life out of my respect that the experts behind it are very open-minded. They have really been pushing the boundaries of our knowledge and imagination.

4) There has been a considerable effort during past several decades trying to understand evolution from a thermodynamical point of view. I believe, if my demonstration is correct, such an effort is doomed to fail, as already suggsested by the names: Evolution is a dynamical process and thermodynamics is not. Put it in a strong way–Properties of thermodnamics are only parts of the evoluiontary dynamics, understood perhaps already by L. Boltzmann more than 100 years ago. This view is explored in my manuscript posted online: http://xxx.lanl.gov/PS_cache/physics/pdf/0512/0512252.pdf.